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Opioid Use and Safety in United States Nursing Homes

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OPIOID USE AND SAFETY IN UNITED STATES NURSING HOMES

A Dissertation Presented

By

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ABSTRACT

Background: Opioids are often used in nursing homes to manage non-malignant pain, but little is known about their long-term use, initiation, and comparative safety.

Methods: We used the Minimum Data Set 3.0 from 2011-2013 merged to Medicare and facility characteristics data to study opioid use and safety among older, long-stay residents. The specific aims were to examine the 1) prevalence of long-term opioid use; 2) geographic variation in the initiation of commonly used opioids (oxycodone, hydrocodone, tramadol); and 3) comparative safety of commonly used opioids and fracture hospitalizations.

Results: One in seven long-stay residents were prescribed opioids long-term. There was extensive geographic variation in the initiation of commonly used opioids, with oxycodone (9.4%) initiated less frequently than hydrocodone (56.2%) or tramadol (34.5%) but varying most extensively across the United States, with the majority of variation in prescribing explained by state of residence. Compared to hydrocodone initiators (7.9 fracture hospitalizations per 100-person years), those initiating tramadol had lower rates of fracture hospitalizations (subdistribution hazard ratio [HR_{SD}] = 0.67, 95% Confidence Interval [CI]: 0.56-0.80), whereas oxycodone initiators had similar rates of fracture hospitalizations (HR_{SD}=1.08, 95% CI: 0.79-1.48).

Conclusion: The prevalence of long-term opioid use was twice as common in nursing homes as community settings, with initiation patterns varying extensively by region and being strongly driven by state of residence. Although initiating tramadol was associated

with lower rates of fractures than hydrocodone, questions on opioid risks and benefits remain and are especially pertinent given the high mortality rates in this population.

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LIST OF ABBREVIATIONS

ADL – activities of daily living
AGS – American Geriatrics Society
BIMS – Brief Interview for Mental Status
CASPER – Certification and Survey Provider Enhanced Reporting
CDC – Centers for Disease Control and Prevention
CI – confidence interval
CMS – Centers for Medicaid and Medicare Services
CPS – Cognitive Performance Scale
CPT-4 – Current Procedural Terminology, 4^{th} edition
ER – extended release
HCPCS – Healthcare Common Procedure Coding System
HHS – Department of Health and Human Services
HRR – hospital referral region
HR_{SD} – subdistribution hazard ratio
ICC – intraclass correlation coefficient
ICD-9 CM – International Classification of Disease, 9^{th} Revision, clinical modification
IPT – inverse probability of treatment
IQR – interquartile range
MBSF – Master Beneficiary Summary File
MDS – Minimum Data Set
NDC – National Drug Codes
NH – nursing home
NSAIDS – nonsteroidal anti-inflammatory drugs
OME – oral morphine equivalent
OR – odds ratio
PCV – proportional change in cluster variation
PPV – positive predictive value
PR – prevalence ratio
PRN – *pro re nata* (“as needed”)
RERI – relative excess risk due to interaction
SD – standard deviation
SMD – standardized mean difference
SNF – skilled nursing facility
US – United States

PREFACE

Some of the work presented or related to this dissertation has been published, is currently under review, or is prepared to be submitted for peer-reviewed publication.

Chapter II:

Hunnicutt JN, Chrysanthopoulou SA, Ulbricht CM, Hume AL, Tjia J, Lapane KL. Prevalence of long-term opioid use in long-stay nursing home residents. J Am Geriatr Soc. 2018; 66:48-55.

Chapter III:

Hunnicutt JN, Baek J, Alcusky M, Hume AL, Liu SH, Ulbricht CM, Tjia J, Lapane KL. Geographic variation in the initiation of commonly used opioids and dosage strength in United States nursing homes. Manuscript under review.

Chapter IV:

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Hunnicutt JN, Ulbricht CM, Tjia J, Lapane KL. Pain and pharmacologic pain management in long-stay nursing home residents. Pain. 2017;158:1091-1099.

Hunnicutt JN, Hume AL, Ulbricht CM, Tjia J, Lapane KL. Long-acting opioid initiation in United States nursing homes. Manuscript under review.

CHAPTER I:

INTRODUCTION

Pain and pharmacologic pain management in United States (US) nursing homes

In United States nursing homes, 35 to 49% of long-stay residents experience intermittent or persistent pain.[1–4] Left untreated or undertreated, pain has distressing and far-reaching consequences including dependence in activities of daily living,[5,6] anxiety,[5,7] depression,[5,7–9] aggressive behavior,[10] decreased involvement in recreational activities,[8,11] and increased healthcare costs.[12,13] Despite this, pain has been historically undertreated in US nursing homes. Many residents receive no analgesics including residents with daily malignant pain at admission (1992-1995: 26% of residents;[14] 2006-2007: 17.5%),[15] daily nonmalignant pain at admission (1992-1995: 25.1%),[5] daily pain at the end of life (1992-1997: 20.2%),[16] and persistent nonmalignant pain (1998-2000: 24.5%;[3] 2008: 16.7%).[17] Although the prevalence of untreated pain appears to be declining over time with recent studies documenting encouragingly lower estimates of administration of no analgesics among residents with cancer-related pain at the end of life (2011-2012: 4.0%)[18] and long-stay residents with persistent pain (2011-2012: 6.4%),[1] little is known about the overall use and safety of commonly-used pharmacologic pain management strategies – including opioids.

Opioid prescribing among older adults – nationwide and in US nursing homes

Pain management guidelines specific to older adults (persons ≥65 years old) recommend that "all patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid

therapy."[13] However, few studies of opioid effectiveness and safety have included nursing home residents,[19–22] highlighting the "geriatric pharmacoparadox" –we know the least about the risks and benefits of medications in persons who need and use them the most. Guidelines currently recommend opioids for chronic pain based on their short-term effectiveness for managing acute pain and the limited availability of safe and effective therapeutic alternatives for pain management.[13,23–25] Although acetaminophen is the recommended first-line medication for pain in older adults,[13] it may be insufficient for adequate pain control, has a maximum daily dose of 4 grams, is contraindicated in persons with liver failure, and must be used with caution in persons with hepatic insufficiency. Nonsteroidal anti-inflammatory drugs (NSAIDS) are not viable alternatives for most older adults due to the potential for increased risk of cardiovascular disease, kidney failure, and gastrointestinal events.[24] Many nonpharmacologic approaches (e.g., cognitive behavioral therapy, exercise therapy)[26] may be ineffective due to the high burden of cognitive impairment in this population, as well as being potentially impractical (e.g., limited staffing and difficulty billing for services). Thus, in many circumstances opioids may be prescribed as the only viable option for pain management in older adults living in nursing homes.

Calls for increased opioid use must however be placed in the context of the ongoing US opioid epidemic. From 1999 to 2010, the overall nationwide use of prescription opioids quadrupled to more than 240 million prescriptions per year.[27] This skyrocketing in prescription opioid use has been accompanied by an alarming rise in opioid misuse and abuse, addiction, and fatal and non-fatal overdoses.[28–30] In 2015, in

response to this growing national epidemic, the Department of Health and Human Services (HHS) initiated a multifaceted national campaign to address the root causes of opioid abuse.[31,32] HHS efforts include creating clear opioid prescribing guidelines and developing and expanding the evidence base to guide the use of opioid medications to treat non-cancer pain.[31] However, recent federal campaigns addressing the opioid abuse epidemic[31,32] and pain management guidelines[33,34] have largely ignored – with few exceptions[13,25] – the use and safety of opioids in older adults. Older adults have an increased prevalence of pain,[35,36] use more analgesics,[37,38] and are at heightened risk for opioid overdoses and other adverse outcomes in comparison to younger adults.[13,34,39] Further, older adults are not immune to the epidemic of drug-related overdoses; between 2013 and 2014 Americans ≥65 years old had the third highest relative increase in drug overdose deaths behind 25-34 and 35-44 years age groups.[28] Older adults in medically supervised settings such as nursing homes may also be at risk for opioid-related adverse events due to suspected medication errors[40,41] and potentially inappropriate prescribing (e.g., the initiation of fentanyl in opioid-naïve residents).[42,43] Yet, little is known about opioid use and safety in this care setting despite increased opioid prescribing among those in pain.[3,5,44]

Nearly two decades ago (1998-2000), 38.4% of nursing home residents experiencing persistent nonmalignant pain were treated with opioids,[3] but more recent studies from 2007-2009 found that 69.2-73.2% of US residents in persistent nonmalignant pain were prescribed opioids.[17,44] However, these studies have not characterized use in the broader nursing home population (i.e., among all residents vs.

restricted to residents in pain) and have rarely described drug regimen-related characteristics that may increase the risk of adverse drug events (e.g., falls and unintentional overdoses)[24,39,45–49] including length of use (short-, medium-, or long-term use), duration of action used (short- vs. long-acting), prescribed dosage strength, and concomitant psychopharmacologic medication use. These drug-regimen-related characteristics are important to understand because they may increase the risk of adverse drug events including falls and unintentional overdoses in this vulnerable population.[24,39,45–49]

Although the opioid crisis is nationwide, there is extensive geographic variation in opioid prescribing and opioid-related mortality among community-dwelling adults,[50–55] raising concerns of inconsistent or inappropriate prescribing practices dependent on place. These studies have however provided no information on opioids prescribed within nursing homes, raising questions on how opioids are initiated and used within this care setting. The type of opioids that residents initiate may impact the quality of pain management and risk of adverse events due to differing pharmacologic profiles including affinity for mu-opioid receptors, elimination half-lives, and bioavailability affecting time to onset of effect, potency, and analgesic duration.[56–58] Beyond specific opioids initiated, the prescribed dosage strength modulates and potentially increases both the analgesic effect of opioids and the risk of adverse opioid-related events that exhibit a strong dose-response relationship (e.g., falls and fractures).[34,58–60] The extent to which specific opioids and prescribed dosage strength initiated geographically vary and potentially co-vary (i.e., the type of opioid initiated is associated with being prescribed high doses) has

implications for both pain management and resident safety and provides further context for how opioids are initiated and used in this care setting.

Commonly prescribed opioids in nursing homes include hydrocodone, oxycodone, and tramadol.[3,44] Understanding which opioids may be safest to prescribe in a frail, elderly population with few pharmacological pain management alternatives may inform safer prescribing and lead to better pain management. Many prescribers assume that the safety profiles of opioids are interchangeable.[61] However, the unique pharmacologic profiles of these commonly used opioids may explain differences in the sedating and constipating effects of different opioids[62–64] and affect the risk of more serious adverse events. In the only study that compared commonly used opioids among community-dwelling older adults,[58] the risk of adverse outcomes within 180 days of follow-up – such as fractures – varied by specific opioid initiated (hydrocodone: 26 fractures per 100 person-years; oxycodone: 25 fractures per 100 person-years, adjusted rate ratio [vs. hydrocodone] =1.02, 95% CI: 0.86-1.21; tramadol: 7 fractures per 100 person-years, adjusted rate ratio [vs. hydrocodone]=0.32, 95% CI: 0.25-0.40). This suggests that different opioids may have different comparative safety profiles. However, this study has not been replicated; had limited information on potential confounders including pain frequency and severity, cognitive impairment, and activities of daily living; and may not be generalizable to nursing home residents who are on average older with more comorbidities, mobility issues, and potentially inappropriate medication use.[65–70] Comparative safety studies focusing on commonly initiated opioids among nursing home residents are needed.

Specific aims

This dissertation uses recent (years 2011-2013), comprehensive, national data to describe and evaluate opioid use and safety among older adults who were long-stay residents living in US nursing homes. The specific aims of this dissertation were:

Aim 1. To evaluate the prevalence of overall and long-term opioid use:

- Estimate the prevalence of overall and long-term opioid use
- Describe and characterize patterns of opioid use, other pharmacologic/nonpharmacologic pain management, and potentially contraindicated medication use by length of opioid use
- Describe variation in long-term opioid use by key resident factors including age, gender, race/ethnicity, cognitive impairment, and physical functioning.

Aim 2. To examine geographic variation in the initiation of commonly used opioids:

- Describe geographic variability in the initiation of commonly used opioids (oxycodone, hydrocodone, tramadol) and prescribed dosage strength
- Quantify the observed geographic variation in opioid prescribing across hospital referral regions after accounting for differences in resident characteristics, facility characteristics, and state of residence
- Examine and contrast the strength of clustering in opioid prescribing practices within states versus within hospital referral regions.
- Estimate the extent to which type of opioid initiated was associated with dosage strength prescribed

Aim 3. To examine the association between the initiation of commonly used opioids (oxycodone, hydrocodone, tramadol) and risk of hospitalization for major fractures.

Overview of study population and data sources

Our study population of interest was Medicare beneficiaries who were long-stay residents in Medicare- or Medicaid-certified nursing homes (~96% of US nursing homes). We focused on long-stay residents because they generally require long-term assistance to manage their chronic comorbidities and declining physical functioning in comparison to short-stay residents who primarily receive rehabilitative care.[71] We excluded residents <65 years old because we were specifically interested in describing opioid use and safety among older adults.[13] Additionally, residents with cancer or those receiving hospice care were excluded because they have differing pain management guidelines in comparison to those with nonmalignant pain.[25,34,72,73] Additional exclusion criteria were applied to each specific aim to increase the validity of our results and are detailed in later chapters.

This dissertation used routinely-collected, federally-required administrative and claims data from Centers for Medicaid and Medicare Services (CMS) during 2011-2013. Resident-level data included the Minimum Data Set (MDS) 3.0 merged to Medicare enrollment (Master Beneficiary Summary File [MBSF]), hospitalization (Part A), outpatient (Part B; available for 2011 only), and pharmacy (Part D) files. Resident data were linked using a unique encrypted beneficiary identifier. Facility-level data included Certification and Survey Provider Enhanced Reporting (CASPER) data and Nursing Home Compare data[74] were merged to resident data using unique facility provider

numbers. Geographic data on hospital referral regions (HRRs) were merged to facility and resident data using a publically available ZIP code to HRR crosswalk.[75] Each of the eight data sources is described further below:

MDS 3.0 (2011-2013): The MDS 3.0 is a federally required clinical assessment of all residents in Medicare or Medicaid certified nursing homes. It has been in effect since October 2010 and uses measures with documented validity and reliability.[76–78] Assessments contain more than 400 items and are administered by registered nurses who review resident medical records and interview residents (when possible), resident proxies (e.g., family members), and direct care staff to provide a comprehensive picture of resident health status including pain, mood, cognitive functioning, physical functioning, psychosocial wellbeing, mood state, disease diagnoses, symptoms, health conditions, and medication use. Comprehensive assessments occur at admission, annually, and whenever there is a significant change in clinical status. Condensed quarterly assessments (with a subset of items) are administered at 90 day intervals between full assessments. We used the MDS 3.0 for all three study aims.

MBSF (2011-2013): The MBSF is an annual file with one record per Medicare beneficiary that provided detail on beneficiary demographics, date of death during the study period (validated by Social Security Administration Files), and monthly indicators of whether the resident was enrolled in Medicare Part A/B/D and Medicare Advantage. The MBSF was used for all three aims.

Medicare Part A (2011-2013): Part A provides health services claims for hospitalizations and skilled nursing facility stays of eligible Medicare beneficiaries

during the study period. Each claim includes dates or periods of service, diagnosis codes, and charges and/or payments. Diagnoses and procedures are coded to the *International Classification of Disease, 9th Revision*, clinical modification (ICD-9 CM) and/or to the Current Procedural Terminology, 4th edition (CPT-4). We used Part A claims to assess fracture and fall hospitalizations and to determine prior skilled nursing facility and hospitalization stays for aim 3.

Medicare Part B (2011): Part B provides outpatient claims of all eligible Medicare beneficiaries submitted on CMS-1500 claims. Claims are predominantly submitted from non-institutional providers (e.g., physicians, physician assistants, nurse practitioners) and free-standing facilities including ambulance providers, laboratories, and emergency departments. Claims include information on diagnosis and procedure codes using ICD-9 CM, CPT-4, or Healthcare Common Procedure Coding System (HCPCS) codes; dates of service; and reimbursement amounts. Part B claims were used to characterize resident comorbidities and emergency department use for aim 2.

Medicare Part D (2011-2013): Part D provides information on prescription claims submitted to CMS during the study period. Part D claims include information on unique National Drug Codes (NDCs), date dispensed, days' supply, drug name, strength, and dosage form. Part D claims were used in all three aims to identify prescribed opioids, alternative pain medications and pain adjuvants, and potential confounders (aim 3).

CASPER (2011-2013): State surveyors conduct federally-required onsite evaluations of nursing homes at least every 15 months or when complaints have been filed. CASPER is a repository of this survey data and provides information on nursing home characteristics,

health inspections, and facility-aggregated patient characteristics. Facility administrators provide information about ownership, size, certification, special services, and information about the case-mix of residents. For all aims, we used CASPER data to exclude certain facilities primarily serving different patient populations (e.g., provider based facilities). For aim 2, we used CASPER to characterize facility characteristics.

Nursing Home Compare (2011): Nursing Home Compare is a quality rating system designed for future residents and their caregivers to find and compare different Medicare- and Medicaid certified nursing homes. Nursing Home Compare uses aggregated MDS and CASPER assessments to rate each nursing home between one (lowest quality) and five (highest quality) stars. Facilities have an overall five-star rating but are also separately rated on health inspections, staffing, and quality measures. These data were used to characterize facility quality for aim 2.

ZIP code to HRR crosswalk (2011): The ZIP code to HRR crosswalk provided by the Dartmouth Atlas Project links geographic data on the hospital referral region in which each facility is located to other resident and facility data sources.[75] A HRR (N=306) is a regional healthcare market containing at least one hospital that performs neurosurgery and major cardiovascular procedures; HRRs can cross state lines and are commonly used in studies of geographic variation in medication prescribing.[54,79,80] For aim 2, these data were used to examine geographic variation across HRRs.

CHAPTER II:

PREVALENCE OF LONG-TERM OPIOID USE IN LONG-STAY NURSING HOME RESIDENTS

ABSTRACT

Background/Objectives: Overall and long-term opioid use among older adults have increased since 1999. Less is known about opioid use in older adults in nursing homes (NHs).

Design: Cross-sectional.

Setting: U.S. NHs (N=13,522)

Participants: Long-stay NH resident Medicare beneficiaries with a Minimum Data Set 3.0 (MDS) assessment between April 1, 2012, and June 30, 2012, and 120 days of follow-up (N=315,949)

Measurements: We used Medicare Part D claims to measure length of opioid use in the 120 days from the index assessment (short-term: ≤30 days, medium-term: >30-89 days, long-term: ≥90 days), adjuvants (e.g., anticonvulsants), and other pain medications (e.g., corticosteroids). MDS assessments in the follow-up period were used to measure nonpharmacologic pain management use. Modified Poisson models were used to estimate adjusted prevalence ratios (aPR) and 95% confidence intervals (CI) for age, gender, race/ethnicity, cognitive and physical impairment and long-term opioid use.

Results: Of all long-stay residents, 32.4% were prescribed any opioid, and 15.5% were prescribed long-term. Opioid users (versus nonusers) were more commonly prescribed

pain adjuvants (32.9% vs. 14.9%), other pain medications (25.5% vs. 11.0%), and nonpharmacological pain management (24.5% vs. 9.3%). Long-term opioid use was higher in women (vs. men, aPR: 1.21, 95% CI: 1.18-1.23) and lower in racial/ethnic minorities (non-Hispanic blacks vs. whites, aPR: 0.93, 95% CI: 0.90-0.94) and those with severe cognitive impairment (vs. no or mild impairment, aPR: 0.82, 95% CI: 0.79-0.83). **Conclusion**: One in 7 NH residents was prescribed opioids long-term. Recent guidelines on opioid prescribing for pain recommend reducing long-term opioid use, but this is challenging in NHs because residents may not benefit from nonpharmacological and nonopioid interventions. Studies to address concerns of opioid safety and effectiveness (e.g., on pain and functional status) in NHs are needed.

INTRODUCTION

In the United States, prescription opioid use quadrupled to >240 million prescriptions annually from 1999-2010.[27] At the same time, rates of opioid misuse, abuse, addiction, and fatal and non-fatal overdoses increased for both younger and older adults.[28,29,81,82] In response to this epidemic, the Centers for Disease Control and Prevention (CDC) released guidelines for managing chronic pain that caution against opioid use and warn that the benefits for improving pain and function must outweigh the risks when prescribing opioids.[34] The short-term effectiveness of opioids for pain management has been documented.[23,83] However, no study has demonstrated that long-term opioid use (≥3 months) is effective while many studies document risks (e.g. falls, fractures, overdoses).[20] Despite this, use of opioids long-term has increased in community-dwelling older adults.[38,53] To our knowledge, no studies have described long-term opioid use in older adults living in nursing homes.

Managing pain in nursing homes is challenging, and this care setting has a documented history of undertreating pain.[1,3,15,17] Prescribers must balance the risks associated with untreated/undertreated pain (e.g., dependence in activities of daily living, anxiety, depression)[5,6,8] with potential risks of opioids. Opioids are prescribed to 60% of nursing home residents in persistent pain.[17,44] Elderly nursing home residents may be uniquely vulnerable to the sedating side effects of opioids (even at therapeutic doses) and adverse drug events due to their older age, frailty, and high burden of comorbidities and polypharmacy in comparison to community-dwelling elders.[70,84–86] Yet, little is known about how opioids and concurrent pharmacologic/nonpharmacologic therapies for pain

are currently being used in nursing homes despite the potential harms associated with long-term opioid use.[20,34]

To date, opioid prescribing guidelines and national campaigns have largely focused on younger adults and community-dwelling elders and may not be applicable to nursing home residents despite the burden of pain and extensive analgesic use in this population.[13,32–34] We conducted a study to: 1) estimate the prevalence of overall and long-term opioid use; 2) describe patterns of opioid and other pharmacologic/nonpharmacologic pain management by length of opioid use; and 3) describe variation in long-term opioid use by key resident factors.

METHODS

Study Design and Data Sources

This cross-sectional study (approved by the University of Massachusetts School Internal Review Board) used routinely-collected, federally-required administrative data from 2012 of all nursing home residents in Medicare- and/or Medicaid-certified nursing homes (the Minimum Data Set [MDS] 3.0; covering ~96% of US nursing homes) merged to facility characteristics data (Certification and Survey Provider Enhanced Reporting) and pharmacy claims (Medicare Part D). The MDS 3.0 is a standardized assessment conducted by trained, registered nurses with 400+ items including medical conditions, cognitive/physical functioning, and pain/pain management.[76–78] Based on medical record review and interviews with staff and direct caregivers, assessments are conducted at admission and quarterly thereafter. Measures have demonstrated validity and reliability ($K \geq 0.78$ for pain management measures).[76]

Study Sample

Our cohort included Medicare beneficiaries who were long-stay residents (>100 consecutive days in nursing home) and had a MDS assessment between 4/1/2012-6/30/2012 (n=602,122). The first eligible assessment was selected. Long-stay residents were included because they generally require extensive, long-term assistance from nursing homes to manage their chronic disabilities.[71] After restricting to those ≥65 years of age without a cancer diagnosis or receiving hospice care, 315,949 residents met inclusion/exclusion criteria applied for practical purposes (e.g., missing data; see **Figure 2.1**).

Opioid Use

We were conceptually interested in opioid use during 120 days of follow-up (starting at index date), which we operationalized using Medicare Part D claims. Part D claims provided information on the generic drug name (used to identify opioids), prescription fill date, days' supply, dosage form, and dosage strength. Opioids were classified by their duration of action (short- vs. long-acting). The number of prescribed opioids during the 120 days of follow-up was calculated. Dosage form was categorized as oral, injection, transdermal, or other.

We estimated cumulative days of opioid use during the 120 day study period based on opioid prescription fill dates plus days' supply, assuming that the opioid was used on the fill date and daily for as long as the medication was prescribed.[87] We assumed that residents with overlapping opioid prescriptions (e.g., filling a second opioid prescription with ≥1 day of opioid use still remaining from the previous prescription)

used both medications simultaneously as prescribed. We categorized opioid use as long-term (≥90 days cumulative use during the 120 days)[45,88], medium-term (31-89 cumulative days), and short-term (1-30 days). We categorized the average daily dose in oral morphine equivalents (OME) using recent CDC guidelines as <50 mg, 50-89 mg, and ≥90 mg OME/day.[34,89]

Part D claims provide no information on the administration of pain medications. Although not specific to opioids, MDS assessments during follow-up (items J0100A and J0100B) were used to broadly describe pain management regimens in the preceding five days as scheduled and/or *pro re nata* (PRN).

Pain Management and Other Medications

Part D claims provided information on the total number of nonopioid medications and alternative analgesics or pain adjuvants prescribed during the 120 day follow-up. Nonopioid pharmacotherapies included prescribed nonsteroidal anti-inflammatory agents (NSAIDS; excluding aspirin). The American Geriatrics Society (AGS) 2009 guidelines[13] were used to identify pain adjuvants and other medications used for pain.

MDS assessments during the follow-up provided information on potentially contraindicated psychopharmacologic medication use in the 7 days preceding the MDS (anxiolytics, hypnotics).[34] We used the MDS because benzodiazepines were not covered by Part D in 2012. We also measured the percentage of residents receiving ≥2 antipsychotics, anxiolytics, and/or hypnotics because concurrent use of ≥2 central nervous system-active medications with opioids can increase the risk of falls/fractures beyond opioid use alone.[20,24]

Guidelines recommend that persons prescribed opioids receive nonpharmacological interventions.[34] MDS 3.0 item J0100C documented receipt of nonpharmacologic pain management in the 5 days before the assessment.[76]

Resident Characteristics

Age, gender, race/ethnicity, and cognitive/physical impairment have been documented to influence opioid use.[1,3,5,14,15,17] Age (65-74 years, 76-84 years, ≥85 years), gender, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic/Latino, Asian, other), physical impairment, and cognitive impairment came from the MDS. Physical impairment was measured using the MDS Activities of Daily Living (ADL) scale.[90] Cognitive impairment was classified using CMS definitions.[2] We also evaluated persistent pain (defined as pain with a duration ≥3 months),[13] and intermittent pain.[1] We considered resident characteristics that may be potential confounders including length of nursing home stay (<1 year, 1-2 years, 2-3 years, ≥3 years), marital status (married vs. other), comorbidities known to cause pain (e.g., arthritis, fractures), and total comorbidity burden (based on MDS 3.0 Section I; categorized into quartiles).

Analysis

Descriptive statistics summarized 1) variation in resident characteristics by age group; 2) medication use and characteristics of use by length of opioid use during follow-up; and 3) length of opioid use by resident characteristics. Modified Poisson models with robust variance estimation (using generalized estimating equations and exchangeable correlation structure) were used to estimate crude and adjusted prevalence ratios (aPR) with 95% confidence intervals (CI) for key resident characteristics and long-term opioid

use.[91] Adjusted analyses included nursing home state and all resident characteristics. We conducted analyses restricted to those in persistent pain to provide further information on this vulnerable subgroup and to compare our results to prior studies.[1,3,17]

In supplemental analyses, we estimated the prevalence of any opioid use in those who were censored (excluding those who died or received hospice care) to examine whether and to what extent selection bias was introduced by requiring residents to have 120 days of available follow-up in the same facility.

RESULTS

The mean age of long-stay residents was 84.4 years (standard deviation [SD]: 8.7); the majority were women (76.2%), non-Hispanic white (80.6%), with a median length of stay of 2.1 years (interquartile range [IQR]: 1.3–3.6; see **Table 2.1**). Most residents were moderately or severely physically and/or cognitively impaired, with higher prevalence of severe cognitive impairment and dementia in older age groups. More than 40% of residents had ≥7 comorbidities, and painful comorbidities including arthritis (32.8%; more prevalent in older groups), anxiety (25.8%), depression (54.5%), and diabetes (31.6%; more prevalent in younger groups) were common. Persistent pain and intermittent pain occurred in 15.5% and 16.1% of residents, respectively.

Thirty-two percent were prescribed any opioids during the 120 day follow-up period, with 10.4%, 6.5%, and 15.5% of all participants prescribed opioids for short-, medium-, and long-term (**Table 2.2**). The most common opioids were hydrocodone (52.6%; see **Appendix 2.1** for further detail), tramadol (31.8%), fentanyl (12.5%) and oxycodone (11.8%). The majority of short-term (99.0%), medium-term (94.5%) and

long-term opioid users (65.7%) were prescribed short-acting opioids only. Long-term opioid users were prescribed more long-acting opioids (34.1% of long-term vs. 1.0% of short-term users) and had higher average daily doses (16.0% of long-term had average daily dose ≥90 mg OME/day vs. 3.3% of short-term). The majority of opioid prescriptions were oral formulations, though nearly one-quarter of long-term users received transdermal prescriptions (fentanyl). The majority of long-term users received scheduled analgesics (97.0%) with 29.5% receiving PRN analgesics. Scheduled analgesic use was lower for short-term (scheduled: 43.5%, PRN: 42.0%) and medium-term users (scheduled: 77.6%, PRN: 47.6%).

The median number of unique nonopioid medications prescribed during 120 days was 12 in opioid users (IQR: 8-16) and 9 in non-users (IQR: 6-12). When examining other medications used during follow-up (**Table 2.2**), 16.1% of residents prescribed opioids had stand-alone prescription NSAIDS claims versus 8.4% of non-users. Pain adjuvants (32.9% of opioid users) and other medications used for pain (25.5% of opioid users) appeared more than twice as common in opioid users versus non-users. Anxiolytics/hypnotics were more common in opioid users than non-users (31.6% vs. 17.5%), as were ≥2 psychopharmacologics (13.1% vs. 8.0%).See **Appendix 2.2** for specific medications.

Nine percent, 19.8%, 26.0%, and 25.4% of non-, short-term, medium-term, and long-term opioid users received nonpharmacological pain management, respectively.

Women (vs. men; overall: 34.1% vs. 26.8%; long-term: 16.7% vs. 11.6%, non-Hispanic whites (vs. non-Hispanic blacks; overall: 33.9% vs. 27.3%; long-term: 16.6%

vs. 11.7%), those with no/mild cognitive impairment (vs. severe impairment; overall: 44.5 vs. 25.4%; long-term: 21.9% vs. 12.1%), and those in persistent pain (vs. no pain; overall: 69.8% vs. 20.5%; long-term: 35.6% vs. 9.6%) appeared to have greater overall opioid and long-term opioid use (**Figure 2.2**).

Table 2.3 shows that resident factors associated with increased prevalence of long-term opioid use included being severely physically impaired (vs. no/mild impairment; aPR: 1.25, 95% CI: 1.22–1.28) or a woman (vs. men; aPR: 1.21, 95% CI: 1.18–1.23). Prevalence of long-term use was lower in racial/ethnic minorities (vs. non-Hispanic whites): non-Hispanic blacks (aPR: 0.93 95% CI: 0.90–0.95), Hispanics (aPR: 0.84, 95% CI: 0.80–0.88), Asians (aPR: 0.69, 95% CI: 0.61–0.77), and other (aPR: 0.89, 95% CI: 0.80–0.99). Prevalence of long-term opioid use was lower in those with moderate to severe cognitive impairment (severe vs. no/mild; aPR: 0.82, 95% CI: 0.79–0.83). When restricting to residents in persistent pain, adjusted prevalence ratios were qualitatively similar albeit attenuated for gender and physical impairment (**Appendix 2.3**).

In supplemental analyses of opioid use in those excluded due to censoring other than death or hospice, overall opioid use was higher than in our analytic sample (41.8% vs. 32.4%). Incorporating those who were censored into our estimate of the prevalence of any opioid use would have shifted our results from 32.4% to 33.7%.

DISCUSSION

We found that nearly one-third of long-stay residents in 2012 were prescribed opioids during the 120 day follow-up, with 1 in 7 residents prescribed opioids long-term.

We identified interesting patterns of nonopioid analgesics, adjuvants, and nonpharmacologic pain management use in opioid users and non-users that begin to fill knowledge gaps in nursing home resident pain management. Although we reported a lower prevalence of persistent pain than older studies,[3,92] the extent to which this is due to the opioids, other medications, or methodologic differences cannot be disentangled.[1] Given no studies demonstrate the long-term effectiveness of opioids and concerns that nursing home residents may be more vulnerable to adverse side effects of opioids,[20,70,84–86] our findings inform discussions about improving opioid use with other pain management strategies in nursing homes.

The high prevalence of long-term opioid use in nursing homes is more than twofold the prescribing seen in community-dwelling older adults.[38,53] This may be warranted due to residents' pain/painful comorbidity burden and the historical undertreatment of pain in this care setting,[1,3,5,14,15,17] which has distressing consequences including poor quality of life, decreased physical functioning, anxiety, and depression.[5,6,8] Similar to community-dwelling populations, most residents received only short-acting opioids.[93] This may be insufficient for managing chronic pain, which may require scheduled, long-acting opioids for adequate pain management.[13] However, the risks of opioid use are not adequately understood, as few studies of opioid effectiveness and safety have examined nursing home residents.[19,20] The high frequency of fentanyl initiation in opioid-naïve residents also raises concerns of suboptimal opioid prescribing.[43,94] In community-dwelling populations, opioids have been linked to falls,

fractures, overdoses, and all-cause mortality; further work is needed to characterize risks in nursing home residents.[20,34]

Our findings suggest that increased use of nonopioid analgesics and nonpharmacologic pain management may be potential areas for improvement in nursing homes, though these recommendations are not without limitations.[13,34] Nonopioid medications used for pain are recommended as the first line treatment for chronic nonmalignant pain and can be concurrently used with opioids to provide potentially greater benefits to residents.[34] We found that pain adjuvants/other medications for pain were only prescribed to approximately half of opioid users during follow-up. Whether this is appropriate remains unclear because these agents also have potential risks. For example, NSAIDS are known to be associated with hepatic, gastrointestinal, renal, and cardiovascular events in older adults and may not be appropriate opioid substitutes.[13,24] AGS and CDC guidelines recommend nonpharmacologic pain management, which can be combined with opioid therapy to provide potentially greater pain relief to residents.[26,34] We found that nonpharmacologic therapies were used in only one-quarter of opioid users. Although we could not ascertain specific nonpharmacologic interventions used with the MDS 3.0, common approaches in nursing homes include bio-feedback, applying heat/cold, massage, physical therapy, nerve block, stretching/strengthening exercises), and electrical stimulation.[95] Their use – along with other nonopioid analgesics – are associated with short-term benefits and lower risks than opioids,[34] but may have limited applicability to cognitively impaired residents and may be difficult to implement given nursing home staffing and reimbursement constraints.

We noted several potentially modifiable risk factors for opioid prescribing, particularly in long-term users. Long-term users had higher daily doses than short- and medium-term users. Although long-term users may need higher doses due to increased opioid tolerance, many adverse events linked to opioids are dose-dependent,[20] and the CDC prescribing guidelines recommend reassessing individual risks and benefits at doses ≥50 OME/day and avoiding or carefully justifying doses ≥90 OME/day.[34] Opioid users had a high prevalence of anxiolytic/hypnotic use. Direct measurement of benzodiazepines was not possible because they were not covered by Part D. Yet, before Part D, benzodiazepine use was more common than other anxiolytics/hypnotics in nursing homes.[96] Benzodiazepines should never be co-prescribed with opioids,[34] though further work is needed to evaluate this issue. Finally, 13% of opioid users received ≥2 medications known to increase the risks of falls/fractures during follow-up (antipsychotics, anxiolytics, and/or hypnotics).[24] When possible, prescribers should optimize concurrent psychopharmacologic use to address concerns of drug-drug interactions and the co-occurrence of anxiety and depression with pain, which can interfere with pain management.[24,34] Although reductions in antipsychotic use have occurred since 2012, antipsychotics, anxiolytics and hypnotics remain commonly used.[97,98]

Findings that long-term opioid use was higher in women, non-Hispanic whites, those with severe physical impairment, and those with no/mild cognitive impairment are consistent with prior studies examining the correlates of untreated or undertreated persistent pain in long-stay residents.[1,17] Contrasting with prior studies,[1,17] we did not

observe a strong relationship between age and opioid use, perhaps due to the higher burden of certain painful comorbidities (e.g., arthritis) in those ≥85 years old, though caution is warranted when using opioids long-term in this population due to residents' increased frailty. Identifying whether some residents are more susceptible to opioid-related adverse events is warranted.

This study has several strengths and limitations. The national MDS 3.0 data linked to Part D claims provided national, comprehensive information on long-stay residents who were Medicare beneficiaries. We provided detailed information on opioid use not previously examined including specific opioids used, dosage strength, and length of opioid use over 120 days of follow-up. We characterized nonopioid pharmacologic alternatives for pain, nonpharmacologic pain management, and concurrent psychopharmacologic medication use. While the data are from 2012, they provide an important, more recent snapshot on opioid prescribing during the height of the opioid epidemic.[1,17,81] Although we had loss to follow-up by requiring residents to be in the nursing home for 120 days, the sensitivity analysis suggests our estimates may be conservative because those lost to follow-up had higher opioid use. We recognize that classifying opioid use by cumulative number of days discarded important information on patterns of opioid use. We believe this affected our results focusing on long-term opioid use minimally. Operationalizing medication use through Part D claims may overestimate opioid use if medications were not used by residents; multiple opioid claims among those prescribed opioids suggest that this issue may be minimal. We cannot know from Part D claims how medications were administered, though data from MDS assessments show

that most long-term opioid users received scheduled analgesics. We have limited information on indications for medication use, resulting in potential misclassification (e.g., medications classified as pain adjuvants when they are prescribed for other indications). We could not evaluate over-the-counter medications from Part D (e.g., over-the-counter NSAIDS). No information on resident or staff pain management preferences was available.

In conclusion, long-term opioid use in older nursing home residents is twice as prevalent than in community settings.[53] Cautious and consistent monitoring of opioid doses, optimizing concurrent psychopharmacologic medications, and increasing use of nonopioid analgesics and adjuvants and nonpharmacologic interventions when appropriate may be warranted to improve the quality opioid use in nursing homes. Interventions to improve opioid prescribing should incorporate complex systems approaches that engage all providers including physicians, nurses, pharmacists, and other staff to improve opioid prescribing (e.g., through education, increased use of alternatives, and adverse event monitoring).[99] Comparative effectiveness studies that focus on physical functioning, pain control, quality of life endpoints, and comparative safety studies of opioids in nursing homes could help healthcare providers, residents, and their families make informed decisions on opioid use.

Table 2.1: Characteristics of long-stay nursing home residents who were Medicare beneficiaries in 2012, overall and stratified by age (N=315,949).

Characteristic, %[1]	Overall (N=315,949)	Stratified by age in years		
		65-74 years (n= 50,005)	75-84 years (n=95,297)	≥85 years (n=170,647)
Women	76.2	55.5	70.8	85.3
Race/ethnicity				
Non-Hispanic white	80.6	73.2	77.3	84.6
Non-Hispanic black	12.6	19.4	14.5	9.5
Hispanic / Latino	4.7	5.5	5.8	3.9
Asian	1.5	1.2	1.6	1.5
Other	0.6	0.8	0.8	0.5
Married	15.7	18.6	21.1	11.8
Length of nursing home stay				
<1 year	17.2	17.9	18.6	16.2
1-2 years	31.1	31.7	32.5	30.1
2-3 years	19.4	18.2	19.4	19.9
>3 years	32.3	32.3	29.6	33.8
Physical impairment[2]				
Moderate	50.9	46.6	49.2	53.2
Severe	25.5	24.3	26.4	25.4
Cognitive impairment[3]				
Moderate	29.4	29.2	29.8	29.3
Severe	44.7	29.8	42.1	50.6
Comorbidities				
Arthritis	30.5	20.6	27.6	35.0
Osteoporosis	19.5	11.6	16.6	23.4
Hip fracture	1.1	0.5	1.0	1.3
Other fracture	1.6	1.1	1.4	1.7
Diabetes	31.6	42.6	37.7	24.9

Dementia	64.5	45.7	64.5	70.0
Parkinson's	7.2	7.7	9.4	5.9
Pressure ulcers	3.0	3.2	3.0	2.9
Anxiety	25.8	26.9	27.0	24.7
Depression	54.5	57.2	56.9	52.5
Asthma, COPD, chronic lung failure	18.3	22.6	19.8	16.2
Respiratory failure	0.6	1.3	0.6	0.3
Renal failure	7.8	8.0	7.8	7.8
>8 total comorbidities[4]	19.1	21.0	20.7	17.8
Pain duration[5]				
Intermittent pain	16.1	15.7	16.0	16.2
Persistent pain	15.5	18.4	16.4	14.1

Abbreviations: BIMS: Brief Interview for Mental Status; COPD: chronic obstructive pulmonary disease; CPS: Cognitive Performance Scale; MDS: Minimum Data Set.

[1]Columns may not add up to 100% due to rounding

[2]Defined using the MDS ADL Self-Performance Hierarchy Scale (range 0-7): None/mild (0-2), moderate (3-4), severe (5-6)

[3]Defined using the BIMS (range 0-15) or CPS (range 0-7): no/mild impairment (BIMS 13-15 or CPS 0-2), moderate (BIMS 8-12 or CPS 3-4), severe (BIMS 0-7 or CPS 5-6)

[4]Total comorbidity burden was defined by summing all comorbidities in MDS 3.0 section I on index assessment and categorizing into quartiles. Only top quartile is displayed.

[5]Defined as any self-reported or staff-assessed pain on both the index MDS assessment and a preceding MDS assessment (90 +/- 20 days before the index assessment)

Table 2.2: Characteristics of opioids, nonopioid pharmacologic alternatives, and potentially contraindicated psychopharmacologic medications prescribed during 120 days of follow-up in long-stay nursing home residents in 2012 (N=315,949).

		Length of opioid use[2]		
Medication use during follow-up[1]	**No opioid use (n=213,652)**	**Short-term (n=32,841)**	**Medium-term (n=20,615)**	**Long-term (n=48,841)**
Opioid use[3]				
Median number opioid claims, (IQR)	-	1 (1-2)	5 (3-7)	6 (5-10)
Duration of action				
Short-acting only	-	99.0	94.5	65.7
Long-acting only	-	0.6	1.8	12.5
Short- and long-acting	-	0.4	3.6	21.8
Average daily dose (in oral morphine equivalents)[4]				
<50 mg /day	-	78.4	77.2	68.1
50-89 mg /day	-	18.4	19.0	15.9
≥90 mg /day	-	3.3	3.8	16.0
Dosage form[5]				
Oral	-	99.5	98.8	91.5
Injection	-	0.2	0.1	0.1
Transdermal	-	0.7	3.6	24.3
Other	-	0.01	0.0	0.0
Nonopioid pharmacologic alternatives				
Standalone prescription NSAIDS	8.4	15.3	17.5	16.0
Any pain adjuvants and/or other medications used for pain[6]	23.4	41.4	50.3	50.3
Pain adjuvants	14.9	27.6	34.7	35.7
Anticonvulsants	9.7	19.7	25.5	25.4
Antidepressants	6.4	11.6	15.6	17.1
Other medications used for pain	11.0	21.8	27.4	27.2
Corticosteroids	6.5	11.2	13.1	12.2
Muscle relaxants	2.7	6.6	9.1	9.6

Transdermal Lidocaine	2.4	6.2	9.2	9.5
Potentially contraindicated medication use[7]				
Any anxiolytic or hypnotic use	17.5	27.6	35.5	32.7
≥2 antipsychotic, anxiolytic and/or hypnotic[7]	8.0	11.5	14.8	13.5

Abbreviations: ER: extended release; IQR: interquartile range; PRN: pro re nata; NSAIDS: nonsteroidal anti-inflammatory agents

[1]Numbers are percentages unless otherwise noted. Percentages may not add up to 100% due to rounding

[2]Based on MDS assessments during follow-up, prevalence of scheduled and PRN analgesics use varied by short- (scheduled: 43.5%, PRN: 42.0%), medium- (scheduled: 77.6%, PRN: 47.6%) and long-term users (scheduled: 97.0%, PRN: 29.5%).

[3]Short-acting opioids included codeine, dihydrocodeine, hydrocodone, hydromorphone, meperidine, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, tapentadol, and tramadol. Long-acting opioids included buprenorphine, butorphanol, transdermal fentanyl, hydromorphone extended release (ER), methadone, morphine ER, oxycodone ER, oxymorphone ER, tapentadol ER, and tramadol ER

[4]Calculated by estimating average daily dose of each unique opioid prescription, converting each prescription to oral morphine equivalents, summing the oral morphine equivalents for all prescriptions, and dividing by the estimated cumulative days of opioid use.

[5]Percentages add up to >100% because some participants used multiple opioids with different dosage forms

[6]Antidepressents commonly used as adjuvants included desipramine, nortriptyline, amitriptyline, duloxetine, venlafaxine and milnacipran.[13] Anticonvulsants included carbamazepine, gabapentin, lamotrigine, pregabalin. Corticosteroids included dexamethasone, prednisone, prednisolone, and methylprednisolone. Muscle relaxants included baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxolone, methocarbamol, orphenadrine, and tizanidine.

[7]Defined using the Minimum Data Set during 120-day follow-up (excludes the index MDS assessment).

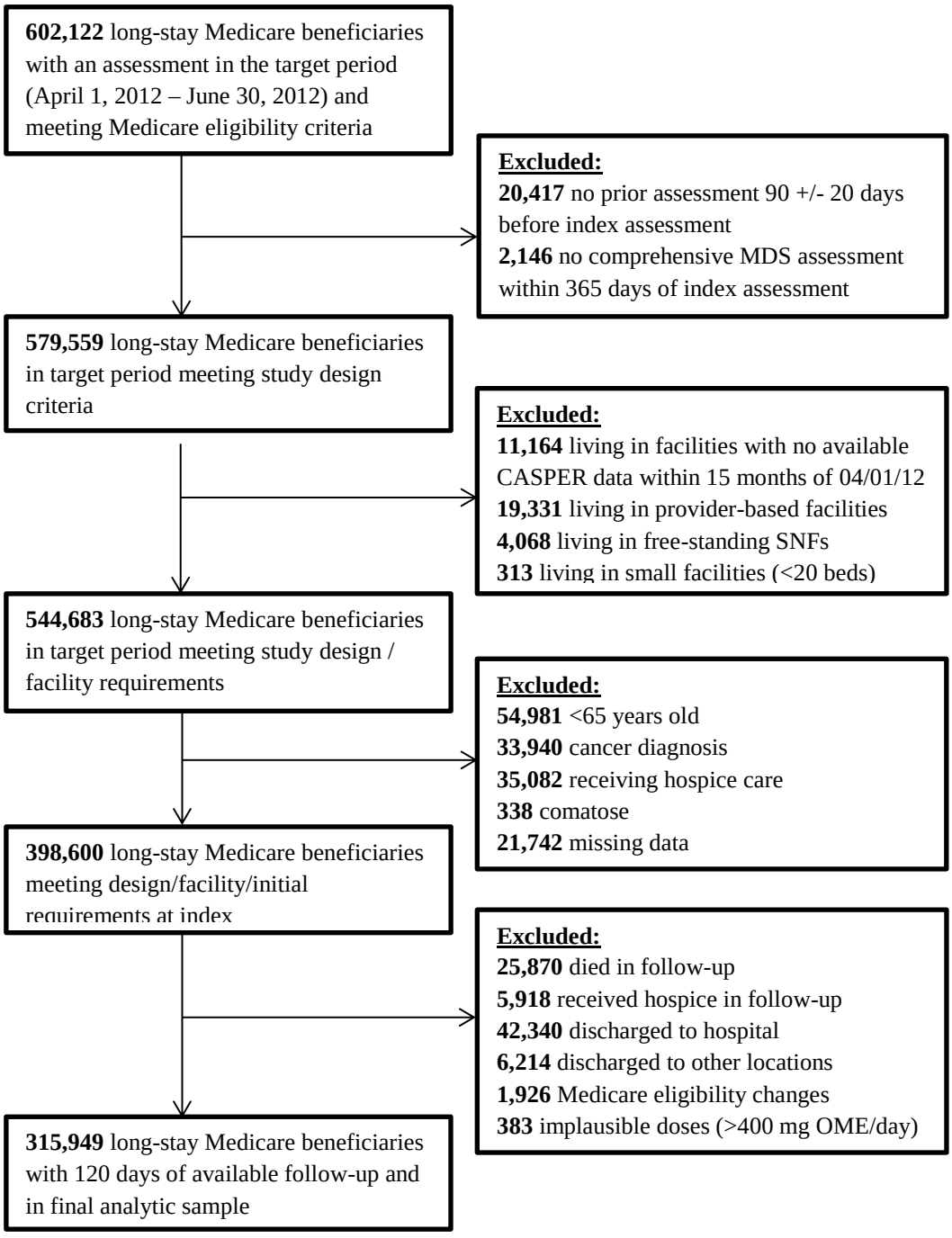
Table 2.3: Association between resident characteristics and long-term opioid use (N=315,949).

Characteristic	Long-term opioid use, %	Crude PR (95% CI)	Adjusted PR[1] (95% CI)
Age, years			
65-74	16.5	Referent	Referent
75-84	15.7	0.93 (0.91–0.95)	0.97 (0.95–1.00)
≥85	15.0	0.88 (0.86–0.90)	0.94 (0.92–0.97)
Gender			
Men	11.6	Referent	Referent
Women	16.7	1.40 (1.37–1.43)	1.21 (1.18–1.23)
Race/ethnicity			
Non-Hispanic White	16.6	Referent	Referent
Non-Hispanic Black	11.7	0.77 (0.75–0.80)	0.93 (0.90–0.95)
Hispanic/Latino	9.4	0.69 (0.66–0.73)	0.84 (0.80–0.88)
Asian	6.4	0.51 (0.46–0.57)	0.69 (0.61–0.77)
Other	12.6	0.81 (0.72–0.90)	0.89 (0.80–0.99)
Cognitive Impairment			
No/mild	21.9	Referent	Referent
Moderate	15.0	0.69 (0.68–0.71)	0.89 (0.87–0.91)
Severe	12.1	0.56 (0.54–0.57)	0.82 (0.79–0.83)
Physical impairment			
No/mild	15.8	Referent	Referent
Moderate	15.1	0.95 (0.93–0.97)	1.04 (1.02–1.06)
Severe	15.9	1.04 (1.02–1.07)	1.25 (1.22–1.28)

Abbreviations: CI: confidence interval; PR: prevalence ratio

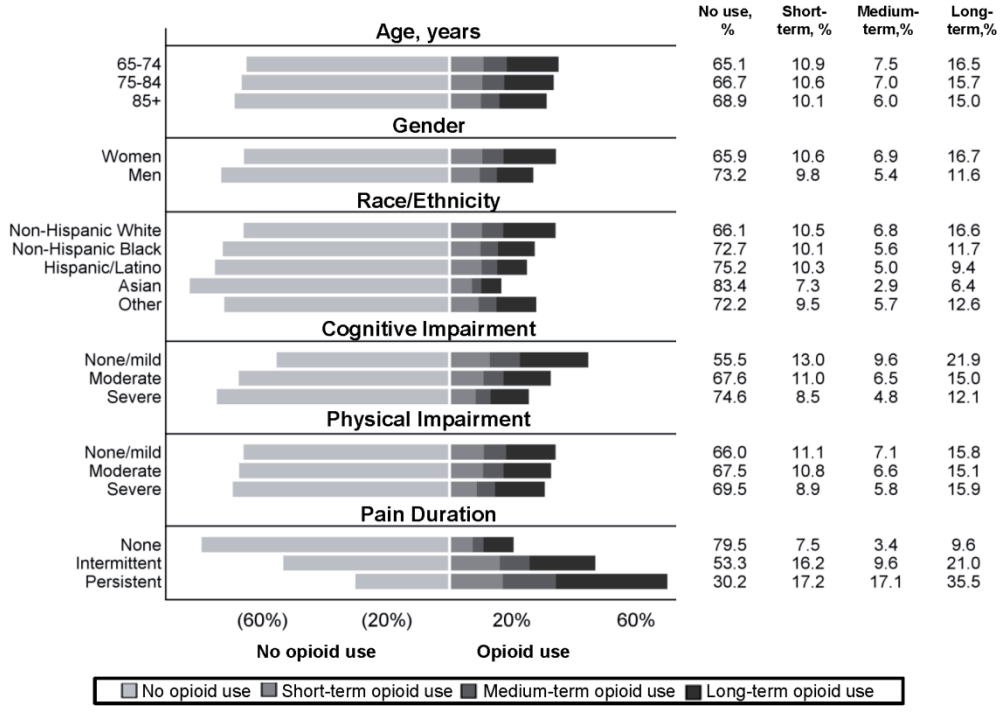
[1]Prevalence ratios were estimated using modified Poisson models (using generalized estimating equations to account for clustering within nursing homes).[91] Models are adjusted for all resident characteristics in Table 1 and state of residence.

Figure 2.1: Selection of participants into study.



Abbreviations: CASPER, Certification and Survey Provider Enhanced Reporting; OME, oral morphine equivalents; SNF, skilled nursing facilities

Figure 2.2: Crude prevalence of short-, medium-, and long-term opioid use by age, gender, race/ethnicity, cognitive impairment, physical impairment, and pain duration for long stay nursing home resident in 2012 (N=315,949).



Chapter III:

GEOGRAPHIC VARIATION IN THE INITIATION OF COMMONLY USED OPIOIDS AND DOSAGE STRENGTH IN UNITED STATES NURSING HOMES

ABSTRACT

Objectives: To examine and quantify geographic variation in the initiation of commonly used opioids and prescribed dosage strength among older United States nursing home residents.

Methods: We merged 2011 Minimum Data Set 3.0 to Medicare claims and facility characteristics data to conduct a cross-sectional study among long-stay nursing home residents who initiated short-acting opioids commonly used in nursing homes (oxycodone, hydrocodone, or tramadol). We examined geographic variation in specific opioids initiated and potentially inappropriate doses (≥50 mg oral morphine equivalents [OME]/day) across hospital referral regions (HRR). Multilevel logistic models quantified the proportional change in between-HRR variation and associations between commonly-initiated opioids and inappropriate doses after adjusting for resident characteristics, facility characteristics, and state.

Results: Oxycodone (9.4%) was initiated less frequently than hydrocodone (56.2%) or tramadol (34.5%) but varied dramatically between HRRs (range: 0-74.5%; most frequently prescribed in HRRs within the Northeast). In total, resident/facility characteristics and state of residence respectively explained 84.1%, 58.2%, 59.1%, and 46.3% of the between-HRR variation for initiating oxycodone, hydrocodone, tramadol,

and inappropriate doses. In all cases, state explained the largest proportion of between-HRR variation. Initiating oxycodone vs. hydrocodone (adjusted odds ratio (aOR) =5.00, 95% Confidence Interval (CI): 4.57-5.47) or tramadol vs. hydrocodone (aOR=0.28, 95% CI: 0.25-0.31) was associated with being prescribed inappropriate doses.

Conclusions: We documented extensive geographic variation in the opioid and dose initiated for nursing home residents, with state explaining the largest proportion of the observed variation. Further work is needed to understand potential drivers of opioid prescribing patterns at the state level.

INTRODUCTION

During the last two decades, prescription opioid use in the United States (US) – along with opioid misuse, abuse, and overdose – dramatically increased in younger and older adults.[27,28,81] The nationwide opioid crisis may be of particular importance in nursing homes, where pain has traditionally been undertreated and long-term opioid use is two-fold the prevalence documented in older community-dwelling adults.[3,14,100] Nationally, extensive geographic variation in opioid prescribing and opioid-related mortality exists, raising concerns about inconsistent and potentially inappropriate prescribing dependent on place.[50–55] However, the extent to which opioid use varies geographically among older adults living in US nursing homes is unknown.

Opioids are often the preferred approach to pain management for nursing home residents due to the limited availability of safe, effective, and practical alternatives.[13,24] Despite this, little is known about the initial choice of opioids prescribed in this setting, and specifically whether there is a preference for short-acting formulations of oxycodone, hydrocodone, or tramadol, the 3 drugs that comprise 90% of short acting opioid use in the nursing home setting.[100] Initial opioid selection may impact the quality of pain management and risk of adverse events due to differing pharmacokinetic and pharmacodynamic profiles (e.g., mu-opioid receptors affinity, elimination half-lives, and bioavailability).[56–58] In addition, little is known about initial choice of prescribed dosage strength, which is important because this modulates and potentially enhances both the

beneficial analgesic effects and the risk of adverse opioid-related events (e.g., fractures).[34]

The extent to which opioid selection and starting dose vary and potentially co-vary may have implications for both the quality of pain management and resident safety. Therefore, we conducted this study to understand the overall patterns and magnitude of geographic variability in the initiation of commonly used opioids and prescribed dosage strength across states and hospital referral regions (HRRs). We then sought to quantify: 1) the extent to which variation across HRRs could be explained by resident characteristics, facility characteristics, and state; 2) the strength of clustering in opioid prescribing practices within states versus within HRRs; and 3) whether the initial opioid choice was associated with differences in dosage strength in terms of oral morphine equivalents (OME).

METHODS

Study design and data sources

This study was approved by the University of Massachusetts Institutional Review Board. Using a cross-sectional study design, nursing home residents "entered" the study on the prescription fill date of their first opioid initiation episode (described further below). The data to identify and characterize residents was drawn from four data sources from 2011: the Minimum Data Set (MDS) 3.0, Medicare (eligibility, Part B, Part D), the Certification and Survey Provider Enhanced Reporting (CASPER), and Nursing Home Compare. The MDS is a federally-required assessment that is conducted by nurses who

interview residents (when possible), resident proxies (e.g., family members), and direct care staff to provide information on residents' pain, cognitive and physical functioning, mood, comorbidities, and other measures.[76–78] Assessments occur at admission, quarterly, and whenever there is a clinical change in status. Medicare Part B was used to operationalize painful comorbidities recorded in outpatient claims. Part D provided information on opioids and other prescribed medications. We used CASPER, a repository for federally mandated nursing home surveys, to provide information on facility characteristics (e.g., number of beds). Nursing Home Compare, a system developed for consumers to find and compare the quality of nursing homes, provided information on facility quality ratings.[74]

Study sample

Shown in **Figure 3.1**, we included long-stay nursing home residents (≥90 consecutive days in the same facility) who were ≥65 years old and initiated a commonly-used opioid (oxycodone, hydrocodone, tramadol).[100] We focused on long-stay residents because they generally require long-term assistance to manage their chronic comorbidities.[71] Our cohort had to have 90 days of Medicare eligibility within 2011 (Part A/B/D coverage; no Medicare Advantage) before initiating a study drug to distinguish between incident and prevalent opioid use. Initiation was defined using Part D claims as being prescribed a study opioid with no opioid prescription claim in the preceding 90 days.

We excluded residents who were hospitalized or received care covered by Medicare Part A during 2011 in the 90 days preceding initiation because medications received during these stays would predominantly be bundled into the Part A per diem rate; therefore, opioid prescriptions during this time would not appear as a Part D claim. We excluded: residents with no MDS assessment in the 90-day lookback period; those living in facilities with no recent CASPER data; residents living in standalone skilled nursing facilities or provider-based facilities; those with cancer or receiving hospice care in the year before initiation; those who were comatose; those with any missing data; those initiating implausibly high doses (>180 mg OME/day); and those living in small geographic areas (states/districts with <50 residents or hospital referral regions with <30 residents). The final sample size was 62,889 residents.

Opioid Use

Commonly used opioids were short-acting, oral formulations of oxycodone (oxycodone, oxycodone/acetaminophen, oxycodone/nonsteroidal anti-inflammatory drug [NSAID]), hydrocodone (hydrocodone/acetaminophen, hydrocodone/NSAID), or tramadol (tramadol, tramadol/acetaminophen). These medications are used by >90% residents prescribed opioids and may be interchangeably used in nursing homes.[100] From medications dispensed on the index date, we estimated the average daily dose in OME. See **Appendix 3.1** for further detail on OME conversion factors and study/non-study opioids).[101] We categorized residents prescribed doses ≥50 mg OME/day as receiving

potentially inappropriately high doses based on recommendations for opioid-naive patients.[34]

Geographic Variation

We first examined geographic variation across US states. We then grouped residents into HRRs because prior studies show substantial variation within-states and across healthcare markets.[54,79,80] A HRR can cross state lines and represents a regional healthcare market containing at least one hospital that performs neurosurgery and major cardiovascular procedures.[75,102]

Resident characteristics

We identified the most recent 2011 MDS assessment in the 90 days preceding opioid initiation to characterize resident demographics (age, gender, race/ethnicity), cognitive impairment (none/mild, moderate, severe),[2] physical limitations (none/mild, moderate, severe),[90] pain (none, self-reported, or staff-assessed; within the five days preceding the MDS assessment) and dementia.

We used Part B claims from the 90 days preceding initiation to describe painful comorbidities including injuries, pressure ulcers, diagnosed chronic pain, abdominal pain, musculoskeletal pain, and neuropathic pain (see **Appendix 3.2** for International Classification of Diseases, ninth revision, clinical modification codes used to classify these conditions); whether residents had any emergency department visits; and number of Part B claims.

Part D claims from the 90 days before opioid initiation were used to classify any prescribed psychopharmacologic medications that may increase the risk of adverse events (antidepressants, antipsychotics) or pain adjuvants (NSAID, anticonvulsants, corticosteroids, muscle relaxants) that may affect type of opioid initiated.[13,34] Because benzodiazepines were not covered by Part D in 2011, we used the resident's MDS assessment before opioid initiation to classify receipt of any anxiolytic or hypnotic administered in the seven days before the assessment.

Facility characteristics

Nursing home facility characteristics are associated with quality of care and may affect prescribing.[103,104] Using CASPER and Nursing Home Compare, we included the following variables: rural location, facility size, ownership, whether the facility was part of a chain, occupancy, proportion of residents within the facility receiving skilled care, proportion of residents with facility-acquired bed sores, proportion of residents restrained, and quartile indicators of the number of minutes per resident day of nursing home staff including registered nurses, physicians, and physician extenders, and overall five-star rating for nursing home quality measures. See **Appendix 3.3** for further detail on how variables were categorized.

Analysis

We first conducted crude and stratified descriptive analyses of resident and facility characteristics by opioid initiated. We then categorized the proportion of residents

initiating different opioids and doses ≥50 mg OME/day into quartiles and generated US maps to visually examine the geographic variation in prescribing by HRR.

We were interested in understanding whether the variation in prescribing observed across HRRs could be explained by resident characteristics, facility characteristics, and state of residence. Thus, we fit multilevel logistic models for each commonly used opioid versus other study opioids (e.g., initiating oxycodone vs. hydrocodone or tramadol) and measured between-HRR variation by incorporating HRRs into the model as random intercepts. We then sequentially fit 4 models for each opioid initiated: 1) null model with only random intercepts for HRRs; 2) adjustment for resident characteristics; 3) adjustment for resident and facility characteristics; and 4) adjustment for resident characteristics, facility characteristics and state.[105] Since HRRs can cross state lines (**Figure 3.2**), we fit cross-classified multilevel logistic models with separate random intercepts for HRRs and states for the final model.[106] For adjusted models, we estimated the proportional change in cluster variation (PCV) to quantify the proportion of between-HRR variation that can be explained by covariates in the model. For example, if adjusting for resident characteristics resulted in a PCV of 10.0% for a specific prescribing practice, we would conclude that 10.0% of the geographic variation was due to differences in resident characteristics between HRRs.

We estimated intraclass correlation coefficients (ICC) for all models to understand the strength of clustering within HRRs (ICC_{HRR}). The ICC_{HRR} measures the correlation among two persons chosen at random from within the same HRR.[105] As the

ICC increases from 0 towards 1, it indicates that residents within the same HRR have an increased propensity to be prescribed the same opioid. For cross-classified models, we decomposed the variance to separately estimate ICC_{HRR} (i.e., the ICC among persons in the same HRR but different states) and ICC_{state}, measuring the strength of clustering for persons in the same states but different HRRs.

To quantify the PCV and ICCs in those initiating doses ≥50 mg OME/day versus lower doses, we used the same sequential multilevel modeling strategy as above. To additionally examine the association between specific opioids initiated and prescribed dosage strength, we fit a separate fully adjusted cross-classified model that included specific opioid initiated to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI). Hydrocodone was chosen as the reference because it was the most commonly initiated study drug. See **Appendix 3.4** for an extended discussion of our multilevel modelling approach.

RESULTS

In 2011, 62,889 long-stay residents initiated opioids (oxycodone: 9.4%; hydrocodone: 56.2; tramadol: 34.5%). These residents lived within 12,345 nursing homes (median residents per home: 4, 25^{th}-75^{th} percentile: 2-7) nested within 298 HRRs (of 306 HRRs; median facilities per HRR: 29, 25^{th}-75^{th} percentile: 16-49); 113 HRRs crossed state lines.

Overall, 53.0% of residents were ≥85 years old, 75.8% were women, and 82.3% were non-Hispanic white (**Table 3.1**; see **Appendix 3.3** for further description of resident

and facility characteristics). Nearly 40% and 21.5% had severe cognitive and physical limitations, respectively. One-third of residents had self-reported or staff-assessed pain, with three-quarters of residents having recorded diagnoses of painful comorbidities from Part B claims. Most residents lived in for-profit facilities (73.1%) with 57.4% being in facilities that were part of a chain.

When stratifying by opioid initiated, those initiating tramadol were more commonly women and ≥85 years old compared to the other initiators. Oxycodone initiators had a lower prevalence of severe cognitive impairment and more self-reported pain on the MDS, as well as painful comorbidities documented in Part B claims than other initiators. Oxycodone initiators were less commonly in facilities that were rural; part of a chain; <80% occupancy; or in the lowest quartiles of registered nurse, physician, and physician extender staffing relative to other opioid initiators.

Several patterns emerged when examining the crude proportion of specific opioids initiated by HRR. The top quartile of oxycodone initiating HRRs was largely concentrated in Northeast states, which contained 18 of the top 20 prescribing HRRs (**Figure 2.3**, **Panel A**). Nationally, the proportion of residents initiating oxycodone ranged from 0% (in 28 different HRRs) to 74.5% in Manhattan, New York (5^{th}-95^{th} percentile, 0-34.7%). Oxycodone was rarely initiated in HRRs within Texas. Alternatively, the top quartile of hydrocodone initiating HRRs largely extended across the middle of the continental US, with prescribing ranging from 3.5% (Bronx, New York) to 90.2% in Redding, California (5^{th}-95^{th} percentile, 23.9-81.1%; **Figure 2, Panel B**).

Tramadol initiation was largely concentrated in Midwest states, Florida, Maryland, and northern New England states (**Figure 2, Panel C),** ranging from 5.8% (Alameda County, California) to 72.1% in Salisbury, Maryland (5^{th}-95^{th} percentile, 12.0%-53.8%).

The overall proportion of residents initially prescribed doses ≥50 mg OME/day was 6.7% with substantial geographic variation (Figure 3). The top quartile of initiators prescribed doses ≥50 mg OME/day was largely concentrated in western US states. However, many HRRs throughout the continental US were in the highest quartile of prescribing, and overall, the practice ranged from 0.0% (4 different HRRs) to 27.6% (Boise, Idaho; 5^{th}-95^{th} percentile, 1.6-14.4%). See **Appendix 3.5** for further detail on prescribed opioid and dosage strength by state.

Resident and facility characteristics explained 7.8%, 1.4%, -2.4% (i.e., an increase in variance), and 8.6% of between-HRR variation for initiating oxycodone, hydrocodone, tramadol, and doses ≥50 mg OME/day, respectively (**Table 3.2**). For initiating oxycodone or doses ≥50 mg OME/day, facility characteristics explained a larger proportion of between-HRR variation than resident characteristics. In all cases, adjusting for state of residence resulted in large reductions in between-HRR variation for oxycodone (PCV=84.1%), hydrocodone (PCV=58.2%), tramadol (PCV=59.1%), and initiating doses ≥50 mg OME/day (PCV=46.3%). In fully adjusted cross-classified models, the propensity to initiate oxycodone was more strongly correlated among two residents in the same state but different HRRs (ICC_{state}=0.24) than among residents within the same HRR but different states (ICC_{HRR}=0.06). These patterns were similar but

less pronounced for the propensity to initiate hydrocodone (ICC_{state}=0.09; ICC_{HRR}=0.07) and tramadol (ICC_{state}=0.09; ICC_{HRR}=0.04). For initiating doses ≥50 mg OME/day the ICCs were similar (ICC_{state}=0.03; ICC_{HRR}=0.03). In general, resident and facility characteristics were weakly associated with opioid or dose initiated, with >85% of the adjusted odds ratios between 0.80-1.20 (See **Appendix 3.6** for further detail on the estimated variance components).

In fully adjusted cross-classified models that included study drug initiated, being prescribed oxycodone versus hydrocodone was associated with increased odds of being prescribed doses ≥50 mg OME/day (aOR=5.00, 95% CI: 4.57-5.47). Initiating tramadol versus hydrocodone was inversely associated with higher doses (aOR=0.28, 95% CI: 0.25-0.31).

DISCUSSION

We found that overall opioid initiation practices among long-stay nursing home residents during 2011 differed from what has been documented in community-dwelling populations,[107,108] with substantial geographic variation in initiating specific opioids and potentially inappropriate doses. In multilevel models, state of residence explained the largest proportion of variation between HRRs, with most opioid prescribing practices more strongly clustered within state than within HRR. Most resident and facility characteristics were weakly associated with prescribing practices in adjusted models. Initiating potentially high inappropriate doses of opioids was associated with choice of starting oxycodone or tramadol versus hydrocodone.

Overall, opioids initiated in nursing homes differ from community settings. Although hydrocodone is initiated similarly across settings,[107,108] tramadol was prescribed to 34.5% of initiators in nursing homes versus 8.7% and 20.2% of commercially insured and Medicare Advantage initiators, respectively.[108] Conversely, oxycodone was prescribed less frequently to nursing home residents initiating opioids (9.4%) compared to 17-18.8% of commercially insured and 16.6% of Medicare Advantage initiators.[107,108] It is unclear how these differences in prescribing affect pain management and safety in nursing homes because most studies exclude nursing home residents and/or compare opioids to placebo rather than conducting head-to-head comparisons of different opioids.[23,58,64,109]

That 1) clustering was stronger within states than HRRs and 2) states explained the majority of variation in opioid prescribing practices across HRRs suggests that factors unique to states and external to HRRs and nursing homes – including laws, policies, and regulations – are strong drivers of how opioids are initiated in this setting. Laws and policies that may have affected prescribing include the implementation of prescription drug monitoring programs, prescription limits restricting the quantity of opioids that can be dispensed, requirements for physician examinations before opioid prescribing, patient identification requirements, pain clinic regulations, and doctor shopping restrictions.[110] These laws drastically increased during 2010-2011[111] and may have affected older nursing home residents even if they were not the primary target of such legislation, as most overdose deaths occur in those <65 years old.[28] However, our results must be

interpreted cautiously, as it was beyond the scope of the current study to examine the role of specific state policies on opioid prescribing.

We found that the proportion of opioid initiators prescribed oxycodone varied more widely between HRRs than other study drugs, with similar geographic patterns documented in younger disabled Medicare beneficiaries.[54] This may be because oxycodone was the only schedule II drug during 2011 and would have been uniquely affected by state laws such as triplicate prescribing programs which are present in low oxycodone prescribing states such as Texas and California. However, there may be additional important state differences in the number, type, and enforcement of laws intended to curb opioid prescribing. For example, among younger commercially insured adults, rescheduling hydrocodone from schedule III to schedule II in 2014 resulted in a larger reduction of hydrocodone prescribing in Texas than in other states.[112] It is unclear if such legislative changes had the same impact on nursing home residents.

Differences in case-mix between HRRs explained little of the observed variation, suggesting that resident characteristics had limited influence on the type and dose of opioid initiated. We are uncertain if such observations are unique to nursing homes because multilevel models have not been used to quantify variation of opioid initiation in other studies. In some cases (being prescribed oxycodone or potentially inappropriate doses), facility characteristics explained a larger proportion of the observed variation than resident characteristics. Facility characteristics may affect prescribing directly (e.g., increased staffing leading to fewer residents initiating inappropriate doses due to

increased oversight) or indirectly through their influence on organizational culture including the shared behaviors, beliefs, values, and assumptions of each facility.[113,114] Further work is needed, but targeting facility culture may be important for improving opioid prescribing.

Overall, residents initiating opioids had a relatively low prevalence of potentially inappropriate doses (6.7%) in nursing homes compared to commercially insured (19.9%) and Medicare Advantage populations (17.0%).[107] That residents predominantly "start low" may be unsurprising given the high prevalence of frailty and concerns of adverse drug events in nursing homes.[69,115] Dose also exhibited less clustering within HRRs and states compared to initiating specific opioids, suggesting that the chosen dose may be less regionally driven than the specific opioid initiated. However, overall geographic patterns of residents initiating higher doses were in many ways similar to patterns documented in community-dwelling adults.[50,52,54] Within the same state and HRR, initiating oxycodone was strongly associated with being prescribed potentially inappropriate doses whereas tramadol was strongly inversely associated with higher doses. These findings may be driven by differences in opioid potency,[89] though further contextualizing the relationship between specific opioids and doses is warranted given that many adverse opioid-related events are dose-dependent.[34]

National efforts to reduce opioid prescribing must not forget that nursing homes have historically undertreated resident pain[3,14] and have only recently shown potential improvements.[1] In this setting, opioids may often be appropriate because older residents

have a high burden of painful comorbidities and lack safe and effective pharmacologic and non-pharmacologic alternatives.[13,100] Further, nursing homes are medically supervised settings where resident access to medication is mediated through staff, which may limit the risk of adverse opioid-related events. Broader national policy changes must consider this vulnerable population so that the pendulum does not swing back towards undertreating pain.

The strengths of this study include focusing on opioid initiation in an important, understudied population; the national, comprehensive data on facility and resident characteristics; and using multilevel models to examine geographic variation. There are also limitations. Data are from 2011, and opioid legislation is rapidly changing. However, we believe it is unlikely that the strong geographic variation observed in this study could dissipate so rapidly. We had limited data on physician characteristics and their contribution to prescribing variation, though we did consider physician staffing as a facility characteristic. Part B claims provided limited information on severity of painful comorbidities. Yet, we were able to supplement these measures with data from the MDS 3.0, including any self- or staff-reported pain, which are not available in traditional claims-based analyses. We assumed that medications were used as prescribed. This is a common assumption[107,108] but may overestimate our potentially inappropriate dose findings if many initiators use opioids as needed. We did not examine the effects of specific state policies. Given our limited follow-up and cross-sectional study design, it was beyond the scope of the current study to examine the influence of state policies. Further work is needed.

Our findings call attention to the complex geographic variation observed by type and dose of opioid initiated in older nursing home residents. The largest driver of observed variation was state of residence, suggesting that state laws, policies, and regulations play the largest role in how opioids are initiated in this setting, though further work is needed to understand how specific laws may affect prescribing in nursing homes. Finally, although the specific opioid initiated was strongly associated with dose and higher doses are associated with increased risks in community dwelling adults,[34] few studies have examined opioid effectiveness and safety in nursing homes, and further work is needed in these areas to guide clinical decision making.

Table 3.1: Individual characteristics of long-stay residents initiating opioids in 2011, overall and stratified by opioid initiated (N=62,889 residents in 12,345 facilities within 298 hospital referral regions).

		Stratified by opioid initiated		
Characteristic[1], %	**Overall (N=62,889)**	**Oxycodone (n=5,891)**	**Hydrocodone (n=35,326)**	**Tramadol (n=21,672)**
Resident characteristics				
≥85 years	53.0	48.6	51.1	57.2
Women	75.8	73.0	74.3	79.1
Race/ethnicity				
Non-Hispanic white	82.3	80.3	82.1	83.2
Non-Hispanic black	11.7	13.7	11.7	11.1
Hispanic/Latino	4.5	4.6	4.5	4.6
Other	1.5	1.4	1.7	1.1
Physical limitations[2]				
Moderate	50.7	52.9	50.5	50.4
Severe	21.5	25.3	21.9	20.0
Cognitive impairment[3]				
Moderate	31.5	31.5	31.5	31.5
Severe	39.5	34.4	40.6	39.2
Psychopharmacologic medications[4]				
Antidepressants	62.3	64.9	63.1	60.4
Antipsychotic	27.5	24.5	28.3	26.9
Antianxiety	21.3	20.5	22.0	20.4
Hypnotics	6.5	6.7	6.7	6.1
Other medications prescribed for pain[4]				
Anticonvulsants	15.5	19.5	15.7	13.9
Corticosteroids	7.2	7.8	7.1	7.1
Muscle relaxants	4.1	5.1	4.3	3.6
Nonsteroidal anti-inflammatory drugs	11.6	10.7	11.2	12.6
Pain recorded on Minimum Data Set[5]				
Any self-reported pain	28.8	33.4	28.6	28.0
Any staff-assessed pain	4.2	4.6	4.5	3.6
Painful comorbidities[5,6]				
Any injury (excludes poisonings)	18.3	22.6	19.0	15.8
Pressure ulcers	7.4	11.3	7.2	6.5
Diagnosed chronic pain	2.7	4.0	2.5	2.6
Abdominal pain	5.5	7.2	5.2	5.3
Musculoskeletal pain	64.0	67.5	62.6	65.4

Neuropathic pain	7.3	8.2	7.3	6.9
Any emergency room use	16.2	18.0	17.7	13.3
Facility characteristics				
Rural location	31.6	19.1	33.6	31.9
≥200 beds	11.0	21.3	9.3	11.0
For profit ownership	73.1	68.2	75.0	71.3
Part of a chain	57.6	49.6	59.1	57.3
<80% occupancy	26.4	16.0	28.4	25.9
<10% of facility receiving skilled nursing care	35.6	34.3	37.1	35.6
1 star nursing home compare quality rating	9.4	8.0	10.0	8.7
≥5% of residents have facility-acquired bed sores[7]	19.2	17.4	19.7	18.8
≥5% of residents restrained[7]	20.5	19.8	21.6	19.1
<27.3 registered nurse minutes per resident day[7]	27.9	17.2	30.1	28.1
<0.3 physician minutes per resident day[7]	25.9	20.1	26.5	26.4
No physician extender minutes per resident day[7]	57.5	51.5	58.6	57.3

[1]Column percentages may not add to 100% due to rounding.
[2]Physical limitations were defined using the Activities of Daily Living Self-Performance Hierarchy (range: 0-6) to categorize residents as having no/mild (0-2), moderate (3-4), or severe limitations (5-6).
[3]Cognitive impairment was defined using the Brief Interview for Mental Status (BIMS; range: 0-15) when the resident could self-report and the Cognitive Performance Scale (CPS; range: 0-6) otherwise: none/mild (BIMS 13-15 or CPS 0-2), moderate (BIMS 8-12 or CPS 3-4) or severe impairment (BIMS 0-7 or CPS 5-6).
[4]Subcategories are not mutually exclusive and may add to >100%.
[5]Derived from the most recent Minimum Data Set assessment preceding opioid initiation.
[6]Based on Part B claims from the 90 days prior to opioid initiation (see Appendix 3.2 for further information on definitions used). The total number of Part B claims (median and interquartile range [IQR]) varied by opioid initiated: hydrocodone (8, IQR: 5-14), oxycodone (11, IQR: 6-18), tramadol (8, IQR: 5-13).
[7]Only lowest staffing quartile shown. See Appendix 3.3 for cutoffs of other quartiles.

Table 3.2: Measuring the proportion change in between-HRR variation explained by resident characteristics, facility characteristics, and state and the strength of clustering within HRRs and state for initiating commonly used opioids or doses ≥50 mg OME/day (N=62,889 residents in 12,345 facilities within 298 hospital referral regions).[1]

	Characteristics included in multilevel model[2]			
	Null model	**Resident**	**Resident + Facility**	**Resident + Facility + State**
Initiating oxycodone				
PCV[3]	Referent	1.3%	7.8%	84.1%
ICC_{HRR}[4]	0.37	0.36	0.35	0.06
ICC_{state}[5]	-	-	-	0.24
Initiating hydrocodone[6]				
PCV	Referent	-2.0%	1.4%	58.2%
ICC_{HRR}	0.16	0.17	0.16	0.07
ICC_{state}	-	-	-	0.09
Initiating tramadol[6]				
PCV	Referent	-3.8%	-2.4%	59.1%
ICC_{HRR}	0.10	0.10	0.10	0.04
ICC_{state}	-	-	-	0.09
Initiating doses ≥50 mg OME/day				
PCV	Referent	1.4%	8.6%	46.3%
ICC_{HRR}	0.06	0.07	0.06	0.03
ICC_{state}	-	-	-	0.03

Abbreviations: HRR, hospital referral region; ICC, Intraclass correlation coefficient; OME; oral morphine equivalent; PCV, proportional change in cluster variation

[1]See Appendix 3.4 for further detail on multilevel model building.

[2]Multilevel logistic models with a random intercept for hospital referral region were sequentially fitted using resident and facility characteristics as described in Appendix 3.3. The final model was a cross-classified multilevel model including a second random intercept for state.

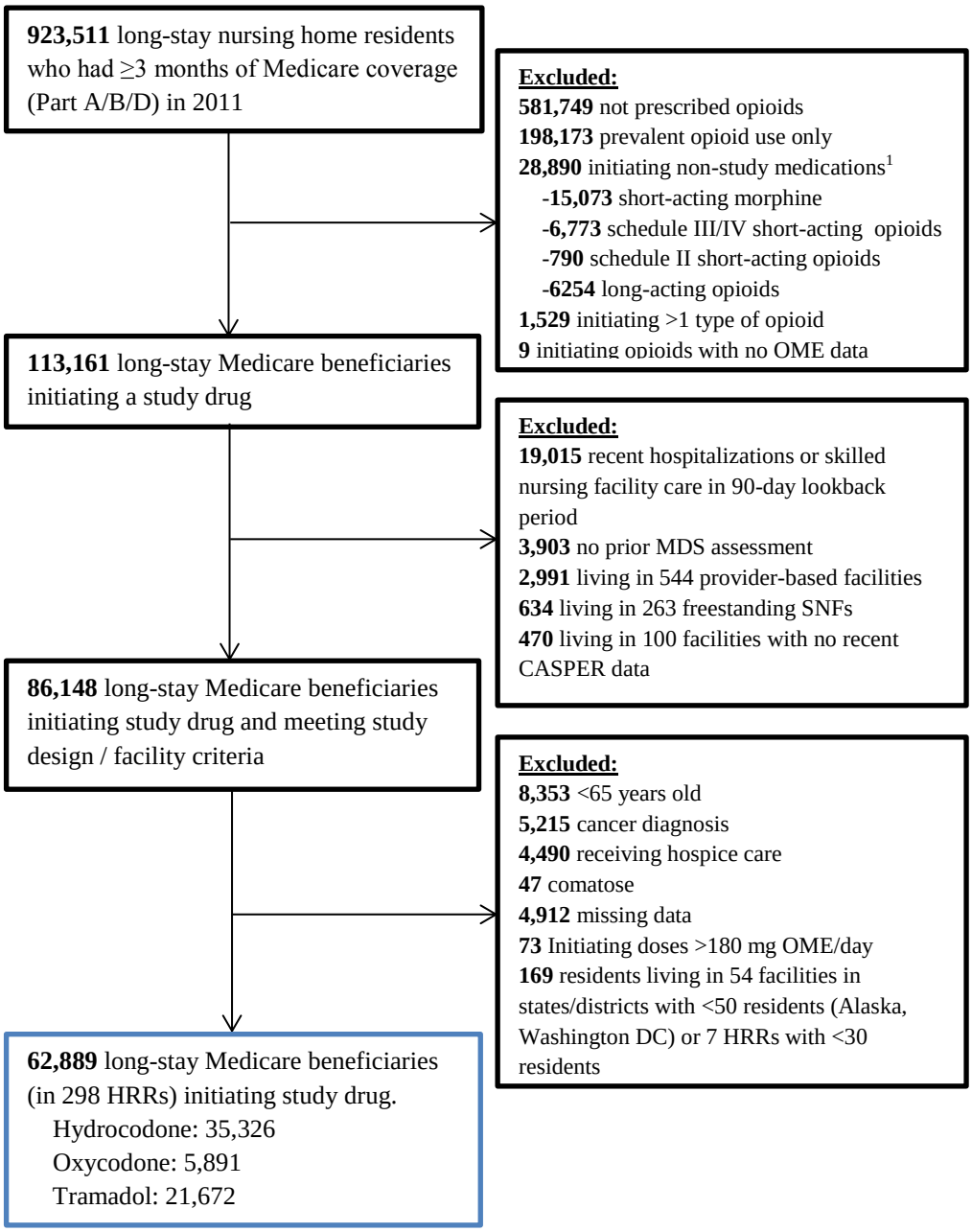
[3]PCV described the proportional change in HRR variation explained by the multilevel model and was estimated as (variance of random intercept in null model – variance of random intercept in adjusted model) / variance of random intercept in null model.

[4]ICC_{HRR} estimates the correlation in the propensity to initiate the same opioid or dose between two individuals randomly selected from each HRR. The ICC_{HRR} for the final model is an estimate of the correlation between two persons in the same HRR but different states.

[5]ICC_{state} was estimated using a cross-classified logistic model and estimates the correlation in the propensity to initiate the same opioid or dose between two individuals in the same state but different HRRs.

[6]Adding resident and facility characteristics to this model increased the variance. This can occur when there is negative correlation between the opioid initiated and resident/facility factors within HRRs.[116]

Figure 3.1: Selection of participants into study.



Abbreviations: CASPER, Certification and Survey Provider Enhanced Reporting; HRR, hospital referral region; OME, oral morphine equivalents; SNF, skilled nursing facilities

[1]Of those initiating non-study drugs, 5,387 short-acting morphine initiators, 3,995 schedule III/IV short-acting opioid initiators, 263 schedule II short-acting opioid initiators, and 1,682 long-acting opioid initiators would have met subsequent eligibility criteria

Figure 3.2: Visualizing the overlap between states and hospital referral regions (HRRs) – Massachusetts as a case study. HRRs (light grey lines) can cross state boundaries (thick black lines) and are therefore not nested within states. Within Massachusetts, there are five unique HRRs (shown in color; see legend), but two – Albany, New York and Providence, Rhode Island – are primarily based in neighboring states. Similarly, two Massachusetts HRRs (Springfield and Boston) extend into neighboring states. This non-nested data structure can be exploited with cross-classified multilevel models to measure the magnitude of clustering within states versus within HRRs and the extent to which variation in opioid prescribing across HRRs is driven by resident characteristics, facility characteristics, and state of residence.

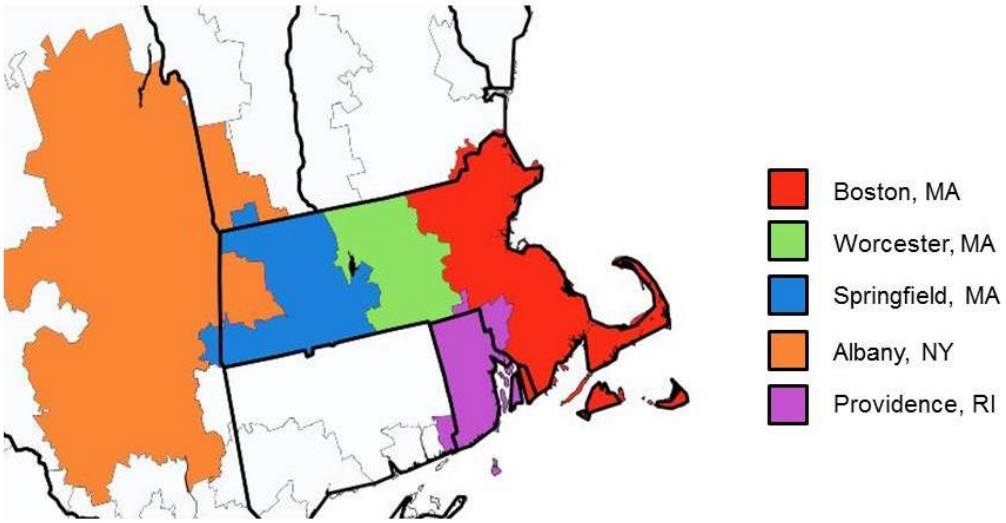


Figure 3.3: Variation in the proportion of commonly used opioids initiated by hospital referral region (N=62,889 residents in 12,345 facilities within 298 hospital referral regions). Panel A, oxycodone; Panel B, hydrocodone; Panel C, tramadol.

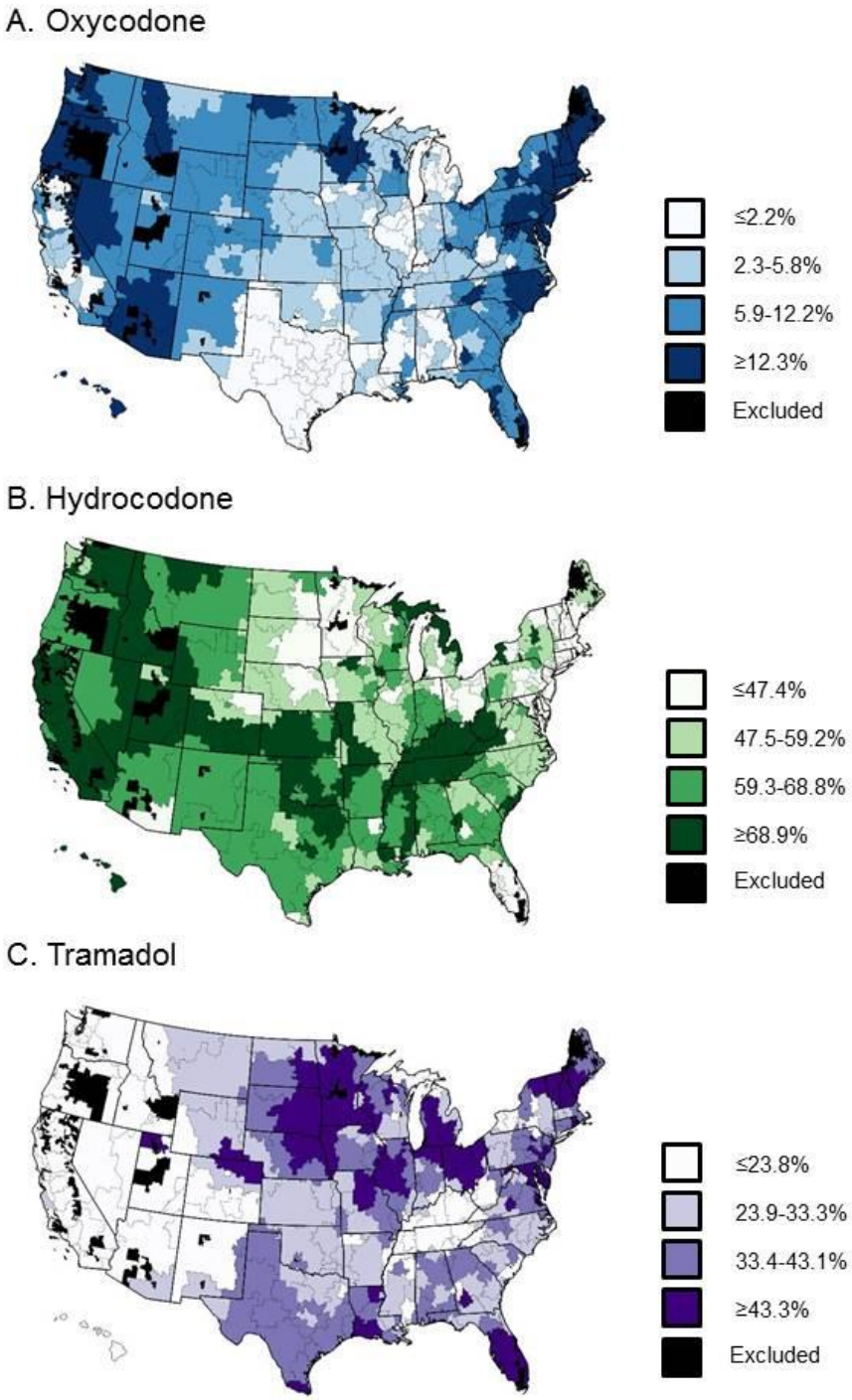
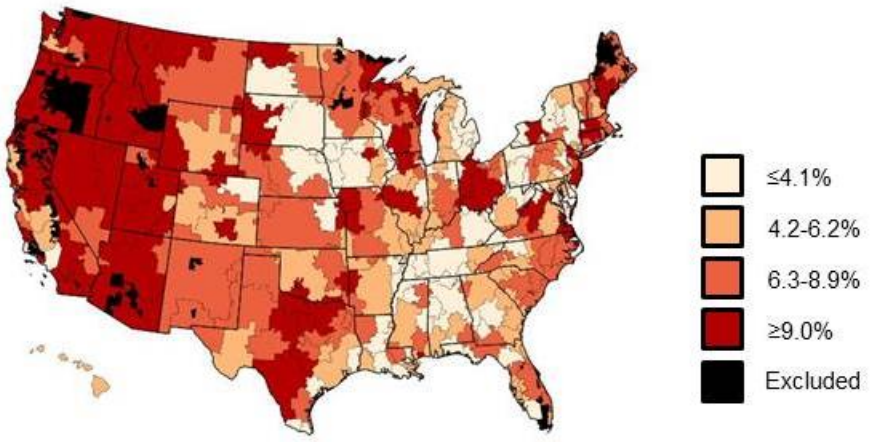


Figure 3.4: Variation in the proportion of residents prescribed doses ≥50 mg OME/day by hospital referral region (N=62,889 residents in 12,345 facilities within 298 hospital referral regions).



CHAPTER IV:

COMMONLY INITIATED OPIOIDS AND RISK OF FRACTURE HOSPITALIZATIONS IN UNITED STATES NURSING HOMES

ABSTRACT

Background: Opioids are commonly initiated in United States nursing homes to manage nonmalignant pain, but there is limited evidence to guide clinical decision-making on which opioid to initiate despite concerns of differing opioid safety profiles, such as fracture risk.

Methods: We conducted a new-user retrospective cohort study of long-stay nursing home residents initiating short-acting oxycodone, hydrocodone, or tramadol by merging the 2011-2013 Minimum Data Set 3.0 to Medicare hospitalization and pharmacy claims. Residents (≥65 years, no cancer or hospice use) contributed treatment episodes (>120 days with no prior opioid claims) and were followed for 180 days until incident fracture hospitalizations (hip, femur, humerus, pelvis, radius/ulna), death (competing risk), treatment changes (e.g., discontinuation), or administrative censoring. Competing risks models were used to estimate subdistribution hazard ratios (HR_{SD}) and 95% confidence intervals (CI). Inverse probability of treatment weighting was used to adjust for baseline confounders.

Results: 110,862 residents contributed 134,432 treatment episodes: 14,373 oxycodone; 69,182 hydrocodone; and 50,877 tramadol initiators. The incidence of fracture hospitalizations per 100 person-years were 9.4 (95% CI: 7.5-11.7) for oxycodone, 7.9 (95% CI: 7.1-8.8) for hydrocodone, and 5.0 (95% CI: 4.3-5.7) for tramadol initiators. In weighted models, oxycodone initiators had a similar rate of fractures as hydrocodone initiators (HR_{SD}=1.08, 95% CI: 0.79-1.48). Tramadol initiators had lower fractures rates than hydrocodone (HR_{SD}=0.67, 95% CI: 0.56-0.80).

Conclusions: The lower rate of fractures that we documented among tramadol initiators compared to hydrocodone initiators is consistent albeit attenuated compared to prior studies among community-dwelling older adults. However, overall fracture rates were lower than in community settings, potentially due to the limited risk of falling in this population with limited mobility. Further work is needed to broaden the evidence base on opioid effectiveness and safety to provide appropriate pain management in nursing homes.

INTRODUCTION

One-third of older United States (US) nursing home residents were prescribed an opioid during 2011-2012 to manage their non-malignant pain.[100,117] Fifteen percent of US nursing home residents were prescribed opioids long-term,[100] more than two-fold the prevalence documented in community settings.[38,53] Acute and long-term opioid use may be necessary in this vulnerable population given the high burden of painful comorbidities and concerns of the consequences of undertreating pain.[5,6,8] Further, these practices are consistent with 2009 American Geriatrics Society guidelines recommending that "all patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy." However, these strong recommendations are supported by limited evidence to guide clinical decision-making on which opioids to initiate, particularly among older, medically-complex nursing home residents.

Short-acting formulations of oxycodone, hydrocodone, and tramadol are prescribed to >80% of residents initiating opioids in US nursing homes.[117] These medications have varying pharmacokinetic and pharmacodynamics profiles including affinity for mu-opioid receptors, metabolic pathways, bio-availability, and elimination half-lives.[56,57,118] Such differences may affect time to onset of effect, potency, duration of analgesia, and ultimately the risk of safety events such as fractures (e.g., by impairing cognition, coordination, and balance leading to falls). In community-dwelling older adults, persons initiating tramadol had lower fracture risk compared to hydrocodone initiators, especially in the first 30 days.[58] Oxycodone initiators had similar fracture risk

to hydrocodone initiators.[58] It is unclear if such findings extend to older nursing home residents due to differences in age, disease burden, polypharmacy, and overall frailty in comparison to community-dwelling adults.[65,84,85,115] Yet, fractures are common and have devastating consequences in nursing homes. Three percent of long-stay residents will experience a hip fracture within two years,[119] with survivors suffering from pressure ulcers and infections, functional decline, and mortality.[120–123] Other fracture hospitalizations may also be devastating but have been understudied in this care setting.

Given the wide use of opioids in nursing homes and residents' increased risk of adverse drug events including fractures, understanding the comparative safety of commonly used opioids in nursing homes is critical. Therefore, we conducted this study to evaluate the risk of major fracture hospitalizations following the initiation of short-acting oxycodone, hydrocodone, or tramadol.

METHODS

The University of Massachusetts Medical School Institutional Review Board approved this study.

Data Sources

We conducted a retrospective cohort study using 2011-2013 Minimum Data Set (MDS) 3.0 merged to the Master Beneficiary Summary File (MBSF; contains Medicare enrollment and death information), Medicare Part A hospitalization claims, and Part D pharmacy claims (including generic drug names, fill date, days' supply, and dosage strength). The Minimum Data Set 3.0 is a federally-required assessment of all US nursing

residents living in US Medicare- and/or Medicaid-certified nursing homes (~96% of all homes). Registered nurses conduct comprehensive assessments at admission, annually, and whenever there is a change in clinical status and at 90 day intervals (using condensed, quarterly assessments with a subset of items) in between comprehensive assessments. Nurses collect information by reviewing residents' medical record and interviewing residents with validated instruments to collect information on comorbidities, cognitive and physical functioning, pain, mood, and other measures.[76–78] MDS 3.0 measures have demonstrated validity and reliability.[76]

Study Population

Our study cohort included Medicare beneficiaries who were long-stay nursing home residents (≥120 consecutive days in facility) and initiated hydrocodone, oxycodone, or tramadol between March 31, 2011 and December 31, 2013. These were the three most commonly used short-acting opioids in nursing homes during the study period.[100] Eligible residents had Medicare Part A, B, and D coverage and no Medicare Advantage plan in the 4 months before initiating hydrocodone, oxycodone, or tramadol.

The unit of analysis was a treatment episode (defined below). As such, residents could contribute multiple treatment episodes if they met our inclusion/exclusion criteria. We excluded treatment episodes with no MDS assessment (quarterly or comprehensive) in the 120 days preceding opioid initiation or no comprehensive assessment in the prior year; those who were recently hospitalized and/or received skilled nursing facility care within 120 days of opioid initiation; those living in provider-based facilities and free-standing skilled nursing facilities; treatment episodes where the resident was <65 years

old at initiation or were comatose, had cancer, received hospice care, or had missing data on potential confounders; and those initiating unusually high opioid doses >180 mg of oral morphine equivalents (OME). To further increase balance of study covariates across treatment groups, we additionally excluded states/districts contributing <100 treatment episodes to the analysis (Alaska, Washington DC) and states where <2% of treatment episodes were oxycodone (Illinois, Michigan, Texas). See **Figure 4.1** for an overview of our study design; see **Appendix 4.1** for further detail on data sources and reasons for inclusion/exclusion criteria.

Opioid Use

Treatment Groups. Our new-user retrospective cohort study compared new initiators of hydrocodone, oxycodone, or tramadol. Between 2011 and 2013, oxycodone was a schedule II medication, hydrocodone a schedule III medication, and tramadol was unscheduled. New initiation was defined as initiating any oral formulation of oxycodone, hydrocodone, or tramadol with no prior use of any opioid in the 120 days before the initiating fill date (index date; see **Appendix 4.2** for further information on study and non-study opioids). Residents were excluded if they were dispensed >1 study drug or both study- and non-study opioids on the index date or initiated an unusually high dose (>180 mg oral morphine equivalents [OME] /day).[124,125]

Initiating Dose. Average daily dose of the oxycodone, hydrocodone, or tramadol prescriptions initiated on the index date was calculated by multiplying dosage strength in OME and quantity dispensed and then dividing by days' supply (**Appendix 4.2**).[89] Doses

were categorized as <25 mg, 25-49, and ≥50 mg OME/day. Although unconventional, these categorizations were chosen because most residents initiate lower doses than community-dwelling adults. Although unconventional, these categorizations were chosen because most residents initiate lower doses than community-dwelling adults,[107,108,117] and doses ≥50 mg OME/day are considered potentially inappropriate in persons initiating opioids for chronic pain.[34]

Follow-up. We were interested in estimating the as-treated effect of commonly initiated opioids on fracture hospitalizations within 180 days of opioid initiation. Residents contributed follow-up time to analyses based on the number of days from the prescription fill date and the earliest of the following: experiencing the study outcome of interest; death (a competing event in analyses of fracture hospitalizations, described below); changes in opioid treatment including discontinuation, switching treatment groups, or initiating a non-study opioid; enrolling in Medicare Advantage; reaching end of follow-up (December 31, 2013); or 180 days of treatment. Residents were assumed to take opioids as prescribed from the fill date through the end of the prescription days' supply. We allotted a seven day grace period between prescription fills (in which a resident was still at risk for the outcome). If a resident filled a subsequent prescription before the calculated end date of the previous prescription, we assumed the new prescription began after the calculated end date of the old prescription. Residents who discontinued initial treatment could reenter (and change treatment groups) if a later treatment episode met eligibility criteria.

Fractures Hospitalizations

The outcome of interest was fracture hospitalizations within 180 days of treatment initiation. We used Part A hospitalization claims using diagnosis and procedure codes to create a composite outcome for major fracture hospitalizations, including femur, hip, humerus, pelvis, or radius/ulna fractures. Although certain fractures (e.g., radius/ulna) may be less likely to results in hospitalization than others (e.g., hip), they are all clinically significant and are among the most common injuries leading to hospitalizations in older adults.[126] External validation studies were used to define fractures using International Classification of Diseases, 9th edition codes (PPV ≥ 87%; see **Appendix 4.3** for specific definitions used).[127–129] If during a treatment episode a resident had multiple fracture hospitalizations, only the first hospitalization was included in the analysis.

Competing Risks

Traditional survival analysis techniques such as Kaplan-Meier curves and Cox proportional hazards models assume that censored study participants have the same survival experience as those remaining in the study.[130] Competing risks violate this assumption because they are events that preclude the study outcome,[131] and analyses that ignore competing risks will overestimate cumulative incidence (the complement of the Kaplan-Meier survival curve). Because residents who die cannot be hospitalized for fractures, we treated death as a competing event, measured using the date of death in the MBSF.

Potential Confounders

Potential confounders were primarily ascertained from Part D claims and the most recent MDS assessment in the 120 days preceding opioid initiation.[132] Because certain chronic comorbidities (e.g., arthritis, osteoporosis) were not included on quarterly assessments, the most recent comprehensive assessment within 365 days preceding opioid initiation was used for these conditions. Prior MDS assessments provided information about state of residence[133] and resident characteristics including demographics (age [included as a continuous variable and quadratic term], gender, race/ethnicity), cognitive impairment,[134] physical functioning,[90] self- or staff-assessed pain, comorbidities associated with falls or fractures, and anxiolytic and hypnotic use (because benzodiazepines were not covered by Medicare during 2011-2012). Part D data were used to identify other medications that may be associated with fractures either directly or as proxies for medical conditions associated with fractures. See **Appendix 4.4** for further detail on resident characteristics included as potential confounders.

Statistical Analysis

We examined the distribution of potential confounders across the three treatment groups and calculated standardized mean differences (SMD) – first by calculating each pairwise treatment contrast and then averaging all 3 treatment contrasts. SMDs measure the differences in means/proportions between treatment groups in units of pooled standard deviation and are uninfluenced by sample size; covariates with SMDs >0.1 are generally considered meaningfully imbalanced.[135]

To adjust for potential confounders, we estimated propensity scores generalized to multiple treatment groups and implemented with inverse probability of treatment (IPT) weighting.[136,137] A propensity score is the probability of treatment given measured covariates and was estimated using a multinomial model that included main terms for state of residence and potential resident confounders. We estimated stabilized IPT weights for each treatment episode by dividing the overall probability of treatment by the resident's propensity of being prescribed the treatment they received.[138] Our IPT-weighting standardized the distribution of measured confounders within each treatment group to that of the entire study population.[139] We evaluated our IPT-weights by comparing the propensity score distributions of initiating each study drug before and after weighting and comparing the SMDs of potential baseline confounder in the crude and weighted sample. [135]

We fit Poisson models to estimate crude and weighted incidence rates of fracture hospitalizations per 100-person years by treatment group. We then fit Fine and Gray competing risks models to estimate crude and weighted cumulative risks and subdistribution hazards ratios (HR_{SD}) for initiating commonly-used opioids on fracture hospitalization risk within 180 days of treatment initiation.[140] For HR_{SD}, robust 95% confidence intervals (CIs) were used to account for weighting and clustering of multiple treatment episodes within residents. We determined that the proportional subdistribution hazards assumption was satisfied after examining the log(-log) transformation of the crude and weighted nonparametric cumulative incidence function.[131] In all analyses, hydrocodone was chosen as the referent treatment because it is most commonly

prescribed opioid in nursing homes and facilitated comparison to prior studies.[58,100] In secondary analyses, we estimated HR_{SD} and cumulative risk over progressively longer periods of follow-up to understand how risk may vary as length of opioid use increased (1-30 days, 1-60 days, 1-90 days).[141]

We conducted stratified analyses by prescribed dosage strength to examine whether the primary associations were modified by initiating dose. Because the specific opioid and dose are simultaneously initiated, we reweighted the data for these analyses as the product of the stabilized treatment IPT-weights (described above) and stabilized dose IPT-weights.[142] Stabilized dose IPT-weights were estimated as the probability of being prescribed the specific dose initiated (<25 mg, 25-49 mg, or ≥50 mg OME/day) and the probability of initiating the specific dose given treatment and previously described confounders in the denominator. We formally tested for additive interaction by estimating the relative excess risk due to interaction (RERI).[143]

We conducted several sensitivity analyses to examine the robustness of our findings: 1) examining the intention-to-treat effect of initiating different opioids within 180 days of treatment initiation; 2) restricting the outcome to hip fracture hospitalizations to potentially enhance the sensitivity and specificity of the outcome definition; 3) restricting to states where ≥10% of treatment episodes were oxycodone because study medications may be more exchangeable in these regions; 4) excluding residents with physical dependence or wheelchair use to examine fracture risk in physically mobile residents; 5) excluding residents with no previously documented pain on the most recent

MDS assessment to mitigate concerns of confounding by pain severity; 6) excluding residents with osteoporosis who may be at increased risk for fractures unrelated to opioid use; and 7) bias analyses to examine the minimum strength an unmeasured confounder would need to have with exposure and outcome on the risk ratio scale to completely explain our primary study results.[144,145]

Our statistical estimates will have a causal interpretation under the following assumptions: consistency; no unmeasured confounding, selection bias, or measurement error; positivity; and correct specification of the weights and outcome model. Although these assumptions are likely violated in practice, we believe this framework provides useful guidance for evaluating our results and the extent to which they can be interpreted causally.[146]

RESULTS

We identified 110,862 long-stay residents (of 1,882,389 long-stay residents in total) who met inclusion criteria and contributed 134,432 treatment episodes to our analysis. Ten percent of initiation episodes were oxycodone, 51.4% were hydrocodone, and 37.9% were tramadol; see **Table 4.1** for further detail on the inclusion and exclusion of initiation episodes by treatment group for each study criteria.

Table 4.2 shows selected unadjusted baseline characteristics and overall IPT-weighted characteristics of the cohort; see **Appendix 4.4** for a complete summary of baseline characteristics in the unweighted and IPT-weighted cohort at baseline. More than half (55.5%) of initiators were ≥85 years old, 47.1% had moderate or severe

cognitive impairment, three-quarters required extensive assistance to manage their activities of daily living or were physically dependent, 29.5% had self- or staff-reported pain at their most recent MDS assessment, and 32.1% were prescribed ≥2 psychoactive medications prior to opioid initiation. Before IPT-weighting, oxycodone initiators were on average younger, more likely to be men, with a lower burden of moderate and severe cognitive impairment, but more physical dependence than tramadol or hydrocodone initiators. IPT-weighting reduced imbalances between groups at baseline by standardizing the distribution of potential measured confounders to that of the entire study cohort. All measured confounders had SMDs ≤0.1 after IPT-weighting. See **Appendix 4.5** for information on the distribution of propensity scores before and after IPT-weighting. See **Appendix 4.6** for detail on SMDs of potential confounders pre- and post-weighting.

Table 4.3 shows the crude incidence rates of major fracture hospitalizations per hundred person-years were 9.4 for oxycodone initiators (77 fractures, 821 person years; 95% CI: 7.5-11.7), 7.9 for hydrocodone initiators (336 fractures, 4,232 person years; 95% CI: 7.1-8.8), and 5.0 for tramadol initiators (209 fractures, 4,197 person-years; 95% CI: 4.3-5.7). Nearly half of hospitalizations were for hip fractures. All-cause mortality during follow-up was common. The crude incidence rate of death among oxycodone initiators (60.9 per 100 person years, 95% CI: 55.7-66.8) was nearly two-fold that of hydrocodone (31.7 per 100 person years, 95% CI: 30.1-33.4) or tramadol initiators (29.1 per 100 person years, 95% CI: 27.5-30.8), 9.7% of initiation episodes were within 90 days of death.

After weighting to reduce differences in baseline confounders between treatment groups, the cumulative risk of fracture hospitalizations during180 days of follow-up was 1.8, 1.6, and 1.1 for oxycodone, hydrocodone, and tramadol initiators, respectively (**Table 4.4**). The HR_{SD} of fracture hospitalizations during 180 days of follow-up was 1.08 for oxycodone initiation versus hydrocodone (95% CI: 0.79-1.48). HR_{SD} estimates were similar when restricting follow-up to shorter time periods. Tramadol was associated with a lower subdistribution hazard of fractures relative to hydrocodone during 180 days of follow-up (HR_{SD}=0.67, 95% CI: 0.56-0.80); these results were consistent when restricting follow-up to shorter time periods.

Oxycodone initiators were more often prescribed doses ≥50 mg OME/day (20.2%) than hydrocodone (6.2%) or tramadol initiators (1.2%). When stratifying by dose, the IPT-weighted HR_{SD} for oxycodone versus hydrocodone (<25 mg OME/day: HR_{SD}=1.36, 95% CI: 0.82-2.28; 25-49 mg OME/day: HR_{SD}=0.89, 95% CI: 0.56-1.41) differed qualitatively, but there was limited evidence of effect modification on the additive scale (RERI=0.45, 95% CI: -0.31-1.21). Dose-stratified HR_{SD} for tramadol versus hydrocodone (<25 mg OME/day: HR_{SD}=0.66, 95% CI: 0.53-0.82 ; 25-49 mg OME/day: HR_{SD}= 0.81) were qualitatively similar with limited evidence of additive effect measure modification (RERI=-0.19, 95% CI: -0.83-0.45). We did not test for effect measure modification in the highest dose strata due to the low number of fracture hospitalizations among oxycodone and tramadol initiators.

Alternative analytic approaches were largely consistent with our primary analyses (**Table 4.5**), though the HR_{SD} between tramadol and fracture hospitalizations relative to hydrocodone were attenuated in the intention-to-treat analyses (HR_{SD}=0.86; 95% CI: 0.76-0.97). When restricting to residents who were not physically dependent or wheelchair users, the IPT-weighted cumulative risk and incidence rates during 180 days of as-treated follow-up increased relative to our primary analysis, especially among oxycodone initiators (cumulative risk: 4.7%; 21.3 fracture hospitalizations per 100 person-years, 95% CI: 11.9-38.2; HR_{SD} in comparison to hydrocodone: 1.55, 95% CI: 0.85-2.85).

In sensitivity analyses examining the robustness of our primary findings to unmeasured confounding, we found that the HR_{SD} between tramadol and fracture hospitalizations during 180 days of as-treated follow-up versus hydrocodone initiation of 0.67 could be explained away by an unmeasured confounder associated with both specific opioid initiated and fracture hospitalization by a risk ratio of 2.35. See **Appendix 4.7** for a range of exposure-confounder and confounder-disease associations needed to explain our primary analyses.

DISCUSSION

Fracture risk may be important to residents and their caregivers when determining which opioid to initiate given their devastating sequelae including reduced quality of life,[122] functional decline,[122] and death.[122,123] In this new-user, IPT-weighted retrospective cohort study, we found that long-stay nursing home residents initiating tramadol had

lower rates of fracture hospitalizations during 180 days of as-treated follow-up, whereas oxycodone initiators had a slightly elevated incidence rate of fracture hospitalizations compared to those initiating hydrocodone (9.6 vs. 8.1 fracture hospitalizations per 100 person-years). These results are largely consistent with a prior study of the comparative safety of opioids in community-dwelling older adults.[58] However, the reduced overall fracture rate that we observed among residents initiating opioids relative to community-dwelling populations[58–60] highlights the uniqueness of opioid use in nursing homes. We believe this work provides further context for weighing the risks when initiating commonly-used opioids, though we also note the limitations of our study and directions for future research.

Our results are consistent albeit less pronounced than Solomon and colleagues' study, which found that community-dwelling elders initiating tramadol had 0.32 times the rate of fractures as matched hydrocodone initiators, and oxycodone initiators had 1.02 times the rate of fractures as hydrocodone initiators.[58] Solomon et al.'s study population had a higher rate of fractures among hydrocodone (26 per 100 person-years), oxycodone (25 per 100 person-years), and tramadol initiators (7 per 100 person-years) than our study population. Although some of this difference may be accounted by how fractures were operationalized (e.g., hospitalization claims alone [current study] versus outpatient and hospitalization claims), the limited mobility of long-stay nursing home residents may lower the association between opioids and fractures,[147] especially if the primary mechanism of action between opioids and fractures among older adults is through acute neurological effects as suggested by prior studies[58–60] rather than hypogonadism or

lowering bone mineral density.[148,149] This was supported by the heightened rates of fracture hospitalizations we observed in analyses restricted to residents without total physical dependence or wheelchair use who had fracture hospitalization rates per 100 person-years ranging from 7.3 (tramadol; HR_{SD} = 0.74, 95% CI: 0.57-0.99) to 21.3 (oxycodone; HR_{SD} versus hydrocodone = 1.55; 95% CI:0.85-2.85). Mobility may matter when evaluating opioid and fracture risk in nursing homes, with higher physical dependence inversely associated with fractures in some[132,150,151] but not all previous studies.[152]

Tramadol is commonly prescribed in nursing homes to manage pain[100,117] and produces analgesia through two mechanisms – weak mu-opioid receptor affinity and serotonin and norepinephrine reuptake inhibition.[57] Because of this unique dual mechanism of action, residents initiating tramadol may on average have lower somnolence, dizziness, and fall risk compared to hydrocodone or oxycodone initiators. However, few head-to-head trials of these commonly used opioids have been conducted to provide further detail on how they may influence fracture risk, particularly among older adults.[20,23] Although tramadol has a similar safety profile to hydrocodone in terms of somnolence and dizziness in younger populations treated for acute pain,[153,154] it is unclear if these findings extend to older adults with chronic pain. Further work is needed to elucidate potential mechanisms by which tramadol and other commonly used opioids may cause adverse events among older nursing home residents.

All opioid initiators in our study had a higher rate a higher rate of fracture hospitalizations (2.8 [tramadol]-3.8 [oxycodone] hip fractures per 100 person-years) than previously reported among long-stay nursing home residents overall (2.3 hip fractures per 100 person-years).[119] This is consistent with prior work in community settings and should be kept in mind when initiating any opioid.[155,156] The risks of other adverse events must also be considered. For example, tramadol is associated with rare but potentially life-threatening adverse drug events including serotonin syndrome and hypoglycemia.[157,158] Finally, nursing home residents are at increased risk of dying compared to community-dwelling adults and may have different goals of care that mitigate concerns of fractures in favor of palliative care. Hydrocodone and tramadol initiators died at slower rates (29.1-31.7 deaths per 100 person-years) than the overall long-stay nursing home population (37.5 per 100 person-years).[119] However, oxycodone initiators were dying at a faster rate (60.9 per 100 person-years); further work is needed to understand whether oxycodone increases mortality risk relative to other opioids as has been documented in community settings.[58]

This study has several unique strengths. We used an active comparator, new-user design to compare three commonly used treatments in nursing homes. This design reduces concerns of confounding by indication and selection bias introduces by comparing incident and prevalent users.[159,160] Compared to prior studies examining fracture risk in older adults,[58–60,155] we had enhanced information from the Minimum Data Set 3.0 on potential confounders including pain, cognitive impairment, and physical functioning that are not normally available in studies relying on Medicare claims alone.

Using IPT-weighting, we achieved good balance of measured baseline confounders; such analytic strategies are not always used despite their advantages when the outcome is rare and there are many potential confounders.[59,156,161]

This study has several limitations that may limit the causal interpretation of our effect estimates. Although we were able to adjust for confounders not normally available in observational research (e.g., physical functioning), we cannot rule out unmeasured confounding. Further, we did not adjust for potential facility-level and other environmental characteristics that may affect fracture risk. In bias analyses, a measured confounder with a risk ratio of 2.35 with both tramadol and fracture hospitalizations would be needed to attenuate our primary finding. This is above and beyond the strength of measured resident- and facility-level confounders with opioid and fractures in this and other studies but is still possible.[117,132,162] We likely undercounted fractures (i.e., reduced sensitivity) by focusing solely on hospitalizations. Our estimates of overall cumulative fracture risk are thus conservative. Our HR_{SD} estimates are expected to be biased towards the null assuming nondifferential misclassification. We assumed that loss to follow-up was nondifferential and examined this assumption by conducting an intention-to-treat analysis; findings were similar albeit attenuated from our primary findings. We measured opioids using claims data and could not distinguish between as-needed (*pro re nata*) or scheduled use. We also assumed that propensity score models and outcome models were correctly specified, though we flexibly parameterized potential confounders (including several categories rather than dichotomizing variables, including higher-order terms for continuous variables) to mitigate these concerns.

In conclusion, we found that initiating tramadol relative to hydrocodone was associated with lower fracture hospitalization risk among older adults living in nursing homes. This may be of particular relevance for persons at heightened risk for falls or who are otherwise concerned about falling. Although this finding is consistent with prior work among community-dwelling older adults, further work is needed to elucidate potential mechanisms. Further, the comparative safety of fractures following opioid initiation must be considered within the broader context of other adverse drug events (e.g., mortality), as well as the unique palliative care needs of this older population.

Table 4.1. Number of persons or treatment episodes meeting study eligibility criteria by study opioid[1]

Study Criteria	Hydrocodone	Oxycodone	Tramadol
1. Long-stay nursing home residents. >120 consecutive days in the same nursing home before study drug initiation.[2]	1,882,389		
2. Medicare eligibility. >120 consecutive days of Medicare Part A, Part B, and Part D follow-up in the 120 day period preceding the index date. Simultaneously, no Medicare Part C (Medicare Advantage) coverage during this period.	1,345,693		
3. New use. No prescribed opioids in the 120 days preceding the index date.	153,695	28,943	101,147
4. No recent SNF care / hospitalizations. No skilled nursing facility care or hospitalization episodes in the 120 days preceding the study index date.	141,001	25,691	93,536
5. Prior MDS assessments. Eligible MDS 3.0 assessment (quarterly or comprehensive) in the 120 day period preceding the index date, and any comprehensive assessment in the year preceding the index date.	121,578	22,355	82,531
6. Facility restrictions. Not residing in a facility with no available CASPER data, stand-alone skilled nursing facility, or provider-based facility on index date.	115,428	21,310	78,943
7. Age ≥65 years. ≥65 years old on the cohort entry date.	103,998	18,952	73,530
8. No cancer. No evidence of cancer, as assessed on prior MDS 3.0 assessments.	97,332	17,284	69,143
9. No hospice. No evidence of prior hospice use, as assessed on prior MDS 3.0 assessments.	90,388	15,673	65,571
10. No comatose. No evidence of being comatose, as assessed on prior MDS 3.0 assessments.	90,338	15,667	65,553
11. No missing data. No missing data on study covariates.	85,052	14,666	62,080
12. Starting dose. Starting dose ≤180 mg oral morphine equivalents.	85,040	14,572	62,080
13. No Small states contributing few residents. Living in states contributing ≥100 treatment episodes to analysis	85,002	14,513	62,048
14. No states with limited oxycodone initiation. Living in states where ≥2% of initiators were prescribed oxycodone	69,182	14,373	50,877

Abbreviations: CASPER, Certification and Survey Provider Enhanced Reports; MDS, Minimum Data Set; SNF, skilled nursing facility.

[1]Criterion 1 and 2 are unique residents; criterion 3-12 are unique treatment episodes.

[2]Further restricted to residents with an available unique encrypted beneficiary identifier.

Note: 110,862 residents contributed 134,432 treatment initiation episodes (17.0% of residents contributed >1 treatment episode [range: 2-6]). Treatment switching was uncommon: 2.4% and 0.01% of residents initiated 2 or 3 different treatments, respectively.

Table 4.2: Baseline characteristics of nursing home residents in the 120 days before initiating oxycodone, hydrocodone, or tramadol (N=110,862 residents; 134,432 treatment episodes)

Characteristic	Crude, stratified by opioid initiated			Overall, IPT-weighted[1]
	Oxycodone	Hydrocodone	Tramadol	
Number of treatment episodes[2]	14,373	69,182	50,877	134,357
Demographics				
Age in years, mean(standard deviation)	83.7 (8.8)	84.3 (8.6)	85.5 (8.4)	84.7 (8.5)
Women, %	72.2	74.5	79.0	76.1
Non-Hispanic white, %	81.0	83.5	84.5	84.1
Married, %	17.5	17.2	15.6	16.7
Behavior, %				
Rejects care	10.2	10.1	9.9	10.0
Wandering	5.0	6.4	6.4	6.2
Cognitive impairment,[3] %				
Moderately impaired	33.6	38.1	37.2	37.0
Severely impaired	10.3	10.1	9.2	9.6
Physical functioning,[4] %				
Requires extensive assistance	55.1	53.1	53.9	53.7
Physical dependence	23.8	21.2	19.5	20.7
Pain,[5] %				
Any self-reported pain	28.1	25.3	25.4	26.1
Any staff-assessed pain	3.8	4.1	3.3	3.7
Urinary incontinence, always %	35.0	31.9	27.7	30.5
Bowel incontinence, always %	29.8	28.0	27.7	26.5
Mobility devices normally used, %				
Cane/walker	45.0	44.0	48.4	46.0
Wheelchair	79.4	75.6	73.9	75.4
Comorbidities, %				
History of falls	21.0	23.4	23.1	23.1
Previous fracture	3.9	2.9	2.7	3.0
Parkinson's disease	6.8	7.4	7.2	7.3
Seizures / epilepsy	8.2	8.2	6.1	7.4
Osteoporosis	18.5	18.5	19.6	18.9
Arthritis	30.2	30.1	33.5	31.7
Pressure ulcers	5.5	3.9	3.3	3.9
Congestive Heart Failure	21.5	21.0	20.7	21.1
Stroke	17.6	17.6	16.7	17.2
Diabetes	35.0	34.5	31.5	33.5
Number of medications prescribed, median	9 (7-13)	9 (7-13)	9 (6-12)	9 (6-13)

(P25-P75)				
Psychotropic medications, %				
≥2 psychotropic medications prescribed[6]	32.2	33.1	30.9	32.3
Antipsychotics	25.1	26.7	25.8	26.2
Antidepressants[7]	64.6	62.7	61.2	62.5
Anxiolytics[8]	20.1	21.3	19.6	20.7
Hypnotics[8]	5.6	5.7	5.1	5.6
Pain adjuvant medications, %				
Anticonvulsants	18.8	15.8	14.1	15.7
Systemic corticosteroids	8.7	7.7	7.9	8.0
Nonsteroidal anti-inflammatory drugs	11.7	11.9	13.1	12.5
Skeletal muscle relaxants	5.6	4.3	3.8	4.4

Abbreviations: IPT; inverse probability of treatment; P25-P75: 25th to 75th percentiles;

[1]Stabilized IPT-weights (mean=1.00, minimum: 0.16, maximum: 8.65) were used to standardize the distribution of potential confounders to that of the entire study population. See Appendix 4.4 for the IPT-weighted distribution of potential confounders by opioid initiated. See Appendix 4.5-4.6 for further detail on the overall distribution of propensity scores and standardized mean differences before and after IPT-weighting.

[2]110,862 residents contributed 134,432 treatment initiation episodes (17.0% of residents contributed >1 treatment episodes [range: 2-6]). Treatment switching was uncommon: 2.4% and 0.01% of residents initiated 2 or 3 different treatments, respectively.

[3]Cognive impairment was defined using the Cognitive Function Scale (CFS; range 0-3): cognitively intact (0), mild impairment (1), moderate impairment (2), and severe impairment.

[4]Physical limitations were defined using the Activities of Daily Living Self-Performance Hierarchy (range: 0-6): no/mild limitations (0-2), extensive limitations (3-4), and physical dependence (5-6).

[5]Resident pain in the five days preceding the most recent Minimum Data Set (MDS) assessment before treatment initiation was based on self-report when the resident was able to and staff assessment otherwise.

[6]Based on antipsychotics, antidepressants, anxiolytics, and hypnotics

[7]See Appendix 4.4 for further detail on specific classes of antidepressants prescribed (e.g., tricyclics) by study drug initiated.

[8]Anxiolytics and hypnotics were measured in the seven days before the most recent MDS assessment because benzodiazepines were not covered by Part D in 2011-2012.

Table 4.3: Crude incidence of first major fracture hospitalizations per 100-person years among nursing home residents initiating oxycodone, tramadol, or hydrocodone; 180 days of as-treated follow-up (N=110,862 residents; 134,432 treatment episodes)

	Oxycodone		Hydrocodone		Tramadol	
Endpoint	**No. of events**	**Incidence Rate[1] (95% CI)**	**No. of events**	**Incidence Rate[1] (95% CI)**	**No. of events**	**Incidence Rate[1] (95% CI)**
Major fracture hospitalization[2]	77	9.4 (7.5-11.7)	336	7.9 (7.1-8.8)	209	5.0 (4.3-5.7)
Hip	35	4.3 (3.1-5.9)	162	3.8 (3.3-4.5)	118	2.8 (2.3-3.4)
Femur	16	1.9 (1.2-3.2)	59	1.4 (1.1-1.8)	30	0.7 (0.5-1.0)
Humerus	18	2.2 (1.4-3.5)	54	1.3 (1.0-1.7)	24	0.6 (0.4-0.9)
Pelvis	-[3]	-[3]	48	1.1 (0.9-1.5)	30	0.7 (0.5-1.0)
Radius/Ulna	-[3]	-[3]	26	0.6 (0.4-0.9)	15	0.4 (0.2-0.6)
Competing risk: Death	500	60.9 (55.7-66.8)	1,343	31.7 (30.1-33.4)	1,220	29.1 (27.5-30.8)

[1]Oxycodone initiators contributed 821 person-years of as-treated follow-up (median follow-up: 14 days; 25th-75th percentiles [P25-P75]: 11-21 days), hydrocodone initiators contributed 4,232 person-years (median: 14 days; P25-P75: 12-22 days), and tramadol initiators contributed 4,197 person-years (median: 15; P25-P75: 12-26).

[2]The total number of specific fracture events exceeds the number of major fracture hospitalizations because 25 initiators were simultaneously hospitalized for ≥2 major fractures.

[3]Rates are suppressed in accordance with Centers for Medicare and Medicaid Service's cell size suppression policy because there were <11 events

Table 4.4: Fracture hospitalizations by opioid initiated among older nursing home residents during as-treated follow-up (N=110,862 residents; 134,432 treatment episodes).

Treatment group	No. of episodes	Crude			IPT-weighted		
		Cumulative risk, %	Incidence rate (95% CI)	HR_{SD} (95% CI)	Cumulative risk, %	Incidence rate (95% CI)	HR_{SD} (95% CI)
Primary Analysis: 1-180 days							
Hydrocodone	69,182	1.5	7.9 (7.1-8.8)	Referent	1.6	8.1 (7.2-9.0)	Referent
Oxycodone	14,373	1.7	9.4 (7.5-11.7)	1.13 (0.88-1.44)	1.8	9.6 (7.1-12.8)	1.08 (0.79-1.48)
Tramadol	50,877	1.1	5.0 (4.3-5.7	0.76 (0.64-0.90)	1.1	4.5 (3.9-5.2)	0.67 (0.56-0.80)
Secondary Analyses							
Restricted follow-up: 1-30 days							
Hydrocodone	69,182	0.6	10.1 (9.0-11.3)	Referent	0.6	9.4 (8.4-10.6)	Referent
Oxycodone	14,373	0.7	11.4 (9.0-14.4)	1.11 (0.86-1.44)	0.6	10.3 (9.6-13.9)	1.04 (0.75-1.43)
Tramadol	50,877	0.4	6.8 (5.9-8.0)	0.72 (0.60-0.87)	0.4	5.1 (4.4-6.0)	0.62 (0.51-0.75)
Restricted follow-up: 1-60 days							
Hydrocodone	69,182	0.8	9.1 (8.2-10.2)	Referent	0.8	9.3 (8.3-10.5)	Referent
Oxycodone	14,373	0.9	10.6 (8.5-13.3)	1.14 (0.88-1.46)	0.9	10.6 (7.9-14.3)	1.10 (0.80-1.51)
Tramadol	50,877	0.6	6.1 (5.2-7.0)	0.74 (0.62-0.88)	0.5	5.3 (4.6-6.2)	0.64 (0.53-0.77)
Restricted follow-up: 1-90 days							
Hydrocodone	69,182	1.0	8.7 (7.8-9.7)	Referent	1.1	8.1 (7.2-9.0)	Referent
Oxycodone	14,373	1.1	10.3 (8.2-12.9)	1.15 (0.90-1.48)	1.2	9.6 (7.1-12.8)	1.09 (0.80-1.50)
Tramadol	50,877	0.7	5.6 (4.9-6.5)	0.74 (0.62-0.89)	0.7	4.5 (3.9-5.2)	0.65 (0.54-0.78)
Dose stratified: <25 mg OME/day[1]							
Hydrocodone	36,246	1.5	6.8 (5.8-11.8)	Referent	1.6	6.9 (5.9-8.0)	Referent
Oxycodone	4,098	2.0	8.3 (5.8-11.8)	1.33 (0.91-1.95)	2.2	9.1 (5.6-14.9)	1.36 (0.82-2.28)
Tramadol	40,899	1.1	4.5 (5.9-7.8)	0.74 (0.60-0.91)	1.1	4.1 (3.5-4.9)	0.66 (0.53-0.82)
Dose stratified: 25-49 mg OME/day[1]							
Hydrocodone	28,616	1.6	10.5 (8.8-12.5)	Referent	1.7	11.0 (9.1-13.3)	Referent
Oxycodone	7,372	1.7	10.6 (7.6-14.7)	1.06 (0.73-1.53)	1.5	9.1 (6.0-13.9)	0.89 (0.56-1.41)
Tramadol	9,374	1.3	8.8 (6.3-12.2)	0.85 (0.58-1.23)	1.4	8.7 (6.1-14.5)	0.81 (0.54-1.21)
Dose stratified: ≥50 mg OME/day[1]							
Hydrocodone	4,320	0.7	9.4 (5.1-17.6)	-[2]	1.3	7.5 (4.2-13.3)	-[2]
Oxycodone	2,903	-[2]	-[2]	-[2]	-[2]	-[2]	-[2]
Tramadol	604	-[2]	-[2]	-[2]	-[2]	-[2]	-[2]

Abbreviations: CI: confidence interval; HR_{SD}: subdistribution hazards ratio; IPT: inverse probability of treatment; OME: oral morphine equivalent

[1] We found no evidence that higher doses (25-49 mg OME/day vs. <25 mg OME/day) increased the subdistribution hazard of fracture risk on the additive scale for hydrocodone and oxycodone (Relative Excess Risk due to Interaction [RERI]=0.45, 95% CI: -0.31-1.21) or hydrocodone and tramadol (RERI=-0.19, 95% CI: -.83-0.45). We did not compare those initiating doses ≥50 mg OME/day to due to the low number of fracture hospitalizations in this group.

[2]Suppressed in accordance with Centers for Medicare and Medicaid Service's cell size suppression policy because there were <11 events.

Table 4.5: Sensitivity Analyses.

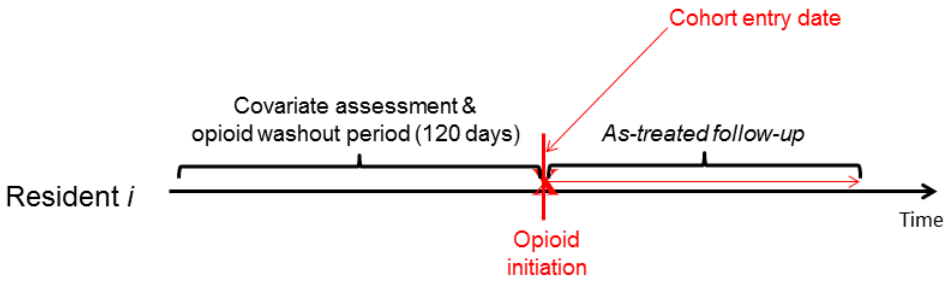
Treatment group	No. of episodes	Crude			IPT-Weighted		
		Cumulative risk, %	Incidence rate (95% CI)	HR_{SD} (95% CI)	Cumulative risk, %	Incidence rate (95% CI)	HR_{SD} (95% CI)
Intention-to-treat analysis[1]							
Hydrocodone	56,375	1.4	3.1 (2.9-3.4)	Referent	1.4	3.2 (2.9-3.4)	Referent
Oxycodone	12,273	1.5	3.6 (3.1-4.2)	1.11 (0.94-1.31)	1.6	3.8 (3.1-4.7)	1.17 (0.93-1.47)
Tramadol	42,214	1.2	2.8 (2.6-3.1)	0.90 (0.80-1.01)	1.2	2.7 (2.5-3.0)	0.86 (0.76-0.97)
Restricting outcome to hip fractures							
Hydrocodone	69,182	0.9	3.8 (3.3-4.5)	Referent	1.0	3.9 (3.3-4.6)	Referent
Oxycodone	14,373	0.9	4.3 (3.1-5.9)	1.05 (0.73-1.51)	1.0	4.6 (3.0-7.1)	1.08 (0.68-1.71)
Tramadol	50,877	0.7	2.8 (2.3-3.4)	0.86 (0.68-1.09)	0.7	2.5 (2.1-3.1)	0.75 (0.59-0.97)
Excluding states where <10% of treatment episodes were oxycodone[2]							
Hydrocodone	15,815	1.1	8.0 (6.4-9.9)	Referent	1.2	7.9 (6.3-10.0)	Referent
Oxycodone	9,298	1.3	9.4 (7.1-12.3)	1.12 (0.79-1.59)	1.4	10.0 (7.4-13.4)	1.18 (0.81-1.71)
Tramadol	15,782	0.9	4.9 (3.8-6.1)	0.76 (0.56-1.05)	0.9	4.5 (3.5-5.8)	0.72 (0.51-1.01)
Excluding residents with physical dependence or wheelchair use							
Hydrocodone	14,422	3.1	13.1 (10.9-15.7)	Referent	3.1	12.5 (10.3-15.1)	Referent
Oxycodone	2,518	4.2	19.4 (13.1-28.5)	1.36 (0.89-2.08)	4.7	21.3 (11.9-38.2)	1.55 (0.85-2.85)
Tramadol	11,982	2.4	8.5 (6.8-10.5)	0.76 (0.57-1.00)	2.2	8.0 (6.4-10.0)	0.74 (0.57-0.99)
Excluding residents without documented pain							
Hydrocodone	20,350	1.4	4.7 (3.7-6.0)	Referent	1.4	4.9 (3.8-6.4)	Referent
Oxycodone	4,593	1.6	5.7 (3.5-9.3)	1.17 (0.68-2.0)	1.6	6.8 (3.2-10.3)	1.11 (0.64-1.93)
Tramadol	14,619	1.1	3.5 (2.6-4.7)	0.83 (0.56-1.23)	1.1	3.3 (2.4-4.5)	0.75 (0.51-1.12)
Excluding residents with osteoporosis							
Hydrocodone	56,397	1.4	7.8 (6.9-8.8)	Referent	1.6	8.0 (7.1-9.1)	Referent
Oxycodone	11,718	1.7	9.6 (7.4-12.2)	1.17 (0.89-1.53)	1.8	9.8 (7.1-13.6)	1.12 (0.85-1.47)
Tramadol	40,918	1.1	4.9 (4.2-5.7)	0.76 (0.62-0.92)	1.1	4.5 (3.8-5.3)	0.67 (0.55-0.82)

Abbreviations: HR_{SD}: subdistribution hazards ratio; IPT: inverse probability of treatment

[1]The sample for the intention-to-treat analysis was restricted to the first initiation episode (n=110,862 residents)

[2]Restricted to the following states: Arizona, Colorado, Connecticut, Delaware, Massachusetts, Maryland, Maine, Minnesota, North Carolina, North Hampshire, New Jersey, New Mexico, Nevada, New York, Oregon, Pennsylvania Rhode Island, Vermont, Washington.

Figure 4.1: Study design overview.



CHAPTER 5: DISCUSSION AND CONCLUSIONS

PURPOSE AND SPECIFIC STUDY QUESTIONS

The overall purpose of this dissertation was to enhance the evidence base on opioid use and safety for non-malignant pain in nursing homes. Specifically, this work was motivated by the following multi-part research questions concerning opioid prescribing among older, long-stay nursing home residents:

Aim 1. What is the prevalence of overall and long-term opioid use?

a. How are opioids prescribed in terms of length of use (i.e., short-, medium-, or long-term durations), duration of action, and average daily dose?
b. What other analgesics, pain adjuvants, and potentially contraindicated medications are concurrently prescribed with opioids?
c. How does the prevalence of long-term opioid use vary by key resident factors including age, gender, race/ethnicity, cognitive impairment, and physical functioning?

Aim 2. Does the initiation of commonly used opioids (short-acting oxycodone, hydrocodone, and tramadol) and prescribed dosage strength geographically vary across hospital referral regions?

a. To what extent is geographic variability due to differences in resident characteristics, facility characteristics, and state of residence across hospital referral regions?

b. Are prescribing practices more strongly clustered within hospital referral regions or states?

c. Does the strength prescribed vary by opioid initiated?

Aim 3. Are there differences in the comparative safety of commonly used opioids and fracture hospitalizations?

a. What are the rates of fracture hospitalizations per 100 person-years in the 180 days following initiation of oxycodone, hydrocodone or tramadol? Do they vary by opioid initiated?

b. Is the association between opioids and fracture hospitalizations modified by dose? To what extent is the association modified by particular analytic decisions (e.g., as-treated vs. intention-to-treat follow-up) or among subgroups at increased risk of fractures (e.g., residents who do not use wheelchairs or are physically dependent)?

This research is especially warranted given the ongoing opioid crisis among younger and older adults and concerns that efforts to contain this epidemic may result in undertreating pain in vulnerable populations.[28,29,81,82] Nationwide, opioid use quadrupled to more than 240 million prescriptions per year from 1999 to 2010.[27] This was accompanied by an alarming rise of opioid misuse and abuse, addiction, and fatal and non-fatal overdoses.[28,29,81,82] Yet, prior trials,[20–22] observational studies,[39,42,45–49] clinical guidelines,[33,34] and federal campaigns[31,32] have largely remained silent on opioid use and safety among older adults, especially nursing home residents. This is concerning given

the higher burden of pain among nursing home residents in comparison to community-dwelling adults,[35,36] much of which may remain undertreated or untreated.[1,3,5,14–17,19,44] Additionally, there are a limited number of alternative pharmacologic and nonpharmacologic options for this older, medically complex population.[13,24,26] Acetaminophen may be insufficient to manage moderate to severe pain, and nonsteroidal anti-inflammatory drugs (NSAIDS) are associated with cardiovascular risks among older adults.[13,24,26] Nonpharmacologic options may be inadequate because of the high burden of cognitive impairment among residents, as well as billing and staffing constraints when implementing such interventions. In many cases, opioids may be the only viable treatment option for pain management, though their use is certainly contentious with some advocating[163,164] and others opposing chronic use.[165] For these reasons, this dissertation addresses an important knowledge gap in the literature and provides further context on use and safety of opioids in nursing homes to help guide clinical and policy decision-making.

SUMMARY OF RESULTS

In aim 1, we conducted a cross-sectional study among older long-stay nursing home residents using data from 2012 to estimate the period prevalence of long-term opioid use and other prescribed analgesics and pain adjuvants during 120 days of follow-up. We found that nearly one-third of long-stay residents were prescribed any opioid, with 1 in 7 residents prescribed opioids long-term. Among long-term opioid users, half were concurrently prescribed alternative analgesics (e.g., NSAIDS) and pain adjuvants,

and 1 in 4 received nonpharmacologic interventions for pain management. Residents who were women (vs. men), non-Hispanic white (vs. racial/ethnic minorities), with no/mild cognitive impairment (vs. those with moderate to severe limitations) or with severe physical limitations (vs. those with no/mild or moderate limitations) had a higher prevalence of long-term opioid use.

In aim 2, we conducted a cross-sectional study among long-stay nursing home residents initiating commonly used short-acting opioids (identified from aim 1; includes short-acting formulations of oxycodone, hydrocodone, and tramadol) to examine geographic variation in opioid prescribing practices including choice of opioid initiated and whether higher doses were prescribed (≥50 mg oral morphine equivalents /day) . We found that more than half of residents initiated hydrocodone (56.2%), 34.5% initiated tramadol and 9.4% initiated oxycodone. We observed strong geographic patterns in opioid prescribing, with the proportion of residents initiating oxycodone being much higher in the Northeast, tramadol being more commonly initiated in the Midwest, and hydrocodone being most commonly prescribed in western US states but also banding across the middle of the continental United States. Seven percent of residents initiated higher doses; this practice was more common in western US states. In multilevel analyses, we found that much of the observed variation in opioid prescribing could not be explained by resident or facility characteristics. However, after additionally adjusting for state of residence, more than half of the variation in specific opioids initiated across hospital referral regions was explained. For higher doses, 46.3% of the variation across hospital referral regions was explained after additionally adjusting for state of residence.

The opioid initiated was strongly associated with dose; for residents within the same state and hospital referral region, initiating oxycodone was strongly associated with being prescribed higher doses in comparison to hydrocodone. Conversely, initiating tramadol was inversely associated with higher doses.

In aim 3, we quantified the comparative safety of commonly-used opioids (oxycodone, hydrocodone, and tramadol) and fracture hospitalizations. Using a new-user retrospective cohort study with inverse probability of treatment weighting to balance baseline confounders, we examined fracture hospitalization risk during 180 days of as-treated follow-up. The incidence rate of fracture hospitalizations was 9.4 per 100 person-years for oxycodone initiators (95% CI: 7.5-11.7), 7.9 per 100 person-years for hydrocodone initiators (95% CI: 7.1-8.8), and 5.0 per 100 person-years for tramadol initiators (95% CI: 4.3-5.7). Using inverse probability of treatment weighted competing risk models, we found that oxycodone initiators had a similar rate of fracture hospitalizations as hydrocodone initiators (subdistribution hazard ratio [HR_{SD}] =1.08, 95% CI: 0.79-1.48) whereas tramadol initiators had a lower rate of fractures compared to hydrocodone (HR_{SD}=0.67, 95% CI: 0.56-0.80). Restricting follow-up to shorter durations (1-30 days, 1-60 days, 1-90 days) showed that the majority of outcomes occurred in the first thirty days though HR_{SD} were similar to the primary analysis. Results were largely consistent during additional sensitivity analyses, though the cumulative risk of fractures was higher in residents who were not wheelchair users or totally physically dependent.

IMPLICATIONS

Clinical Implications. Long-term opioid use in nursing homes is twofold the prevalence documented in older community-dwelling adults.[38,53] This finding from aim 1 highlights the extensiveness of opioids for managing pain in nursing homes. Long-term opioid use in community settings is associated with overdose and death,[20,34] but these findings may not extend to nursing homes residents because access to opioids is mediated through staff, and residents should (in ideal circumstances) be closely monitored by staff to reduce the risk or mitigate the consequences of adverse drug events. Further, long-term use may even be warranted given the prevalence of pain and painful comorbidities,[35,36] risk and consequences of undertreating pain[1,3,5,6,8,14–17,19,44] and limited alternative pharmacologic and nonpharmacologic pain management options.[13,24,26] However, we also documented several areas for potential improvement. Long-term opioid users were prescribed high daily doses that may be potentially worrisome given that the risks of many adverse opioid related events are typically heightened at increased doses (e.g., doses ≥90 mg OME/day).[34] Many long-stay residents were also concurrently prescribed contraindicated psychopharmacologic medications (e.g., antipsychotics, anxiolytics) which may interact with opioids and increase the risk of adverse events such as falls/fractures.[24] Although some of these practices may be declining in response to recent Centers for Medicare and Medicaid Service policies (e.g., the National Partnership to Improve Dementia Care in Nursing Homes and declining prevalence of antipsychotic use, enacted March 29, 2012),[166] risk is nonetheless worrisome given that high psychopharmacologic use continues to be largely endemic in this care setting.[167,168] Potential interventions to improve nursing home prescribing culture[113,114] may thus be

warranted and have shown some success (e.g., improving how staff interact with cognitively impaired residents to reduce antipsychotic use).[98]

Our work on opioid initiation (aims 2 and 3) provided several clinical insights. First, our results suggest that nursing homes largely follow the geriatric maxim of "start low and go slow," because most residents initiated lower doses. This is encouraging given the association of higher doses with adverse events such as fractures and injuries in community-dwelling older adults.[59,169] Second, we found that initiating tramadol was associated with lower fracture hospitalization risk than hydrocodone or oxycodone. This finding is consistent with prior work among community-dwelling older adults that found tramadol to be associated with lower rates of fractures.[58] Third, overall fracture hospitalization rates were lower in nursing home residents than community-dwelling older adults.[58–60] This may be due to the limited mobility of residents, which should be considered when initiating opioids given the increased risk of fractures that we documented in this subset of our study population. Fourth, the risk of death in our population was much higher than community-dwelling elders[58,60] (though largely similar to other long-stay residents)[119] and may reduce concerns of fracture risks in favor of the perceived benefits of different opioids, though we note that there is also limited evidence to guide clinical decision making on the comparative effectiveness of commonly used opioids in this setting.

Policy Implications. Only a quarter of long-term opioid users received nonpharmacologic interventions (e.g., biofeedback, applying heat and cold, massage,

physical therapy, nerve block, stretching and strengthening exercises). Although the efficacy of many nonpharmacologic interventions may be reduced in the presence of moderate to severe cognitive impairment, some therapies may still be efficacious and/or reduce the overall reliance on opioids (e.g., reducing the average dose to a safer range).[34] However, nonpharmacologic interventions are difficult to implement because of limitations with reimbursement, as well as staffing constraints including limited training in palliative care, understaffing, and high staff turnover.[103,170] Financial resources/incentives may thus be needed if clinicians and policymakers seek to reduce opioid use in nursing homes by substituting nonpharmacologic interventions for opioid prescribing. These efforts may also be criticized by the limited evidence on the relative benefit of simultaneous pharmacologic and nonpharmacologic therapies versus pharmacotherapy alone among older nursing home residents.

In aim 2, we found that much of the geographic variation in opioid prescribing across hospital referral regions was driven by state of residence. This suggests that state policies and laws have the largest influence on opioid prescribing and raises concerns that state efforts to curtail opioid prescribing in response to the opioid crisis may affect nursing home residents.[112] As we have noted throughout this work, residents have unique care needs and have historically had their pain undertreated.[1,3,5,14–16,19,44] Efforts to combat the opioid crisis should thus keep the unique needs of this important and oft forgotten population in mind. Otherwise, we risk encouraging devastating, historic norms that disserve some of the most vulnerable among us.

STRENGTHS

This dissertation has several strengths. For all aims, we linked the Minimum Data Set (MDS) 3.0 to Medicare claims. Since the MDS is federally required for all residents living in Medicare- or Medicaid-certified US nursing homes (>96% of all NHs), we were able to comprehensively look at opioid use and safety in long-stay residents across the United States. [76–78] Additionally, the revised MDS 3.0 improved on previous MDS versions by including self-reported measures of pain, mood, and cognitive status, as well as other resident-level measures not traditionally available in pharmacoepidemiologic studies such as physical functioning. Finally, using these national data sources resulted in a large sample size that allowed us to examine uncommon drug utilization patterns and rare outcomes such as fractures while providing sufficient precision to be relevant to potential stakeholders.

Aim 1 improved on many prior studies of pain management in nursing homes.[1,3,5,14–17,19,44] We examined opioid use over a longer window of time than prior studies. We also did not restrict our study population to those reporting pain. We were thus able to provide a more comprehensive summary of how opioids are used to manage nonmalignant pain, which may be either present and underreported or well managed among residents reporting or observed to be in no pain. To our knowledge, we were the first study to use oral morphine equivalents to describe opioid dose in US nursing homes, with prior studies providing limited or no information on dose. We also included tramadol as an opioid in our study. Tramadol was initially approved by the Food and

Drug Administration in 1995 but has been excluded from many studies of pain management in nursing homes despite being the second most commonly used opioid in this work. Finally, we comprehensively measured adjuvants, potentially contraindicated medication use, and nonpharmacologic pain management concurrently used during follow-up to provide further detail on complementary and/or alternative analgesics used during opioid therapy, though adjuvant use has also been examined in other studies.[15,17]

For aim 2, we provided the first examination of geographic variation in opioid prescribing practices among long-stay nursing home residents. Our explicit focus on the initiation of commonly used opioids offered advantages when considering the role of facility characteristics and state of residence, which may exert more influence on prescribing practices at initiation rather than prevalent measures of opioid use. Further, comparing residents at opioid initiation may reduce bias that routinely occurs when comparing incident and prevalent users,[171] as initiators and long-term users likely differ in many important and unmeasurable ways by being at different points in their therapy. Finally, we implemented cross-classified multilevel models,[106,172] which allowed us to leverage the non-nested data structure of states and hospital referral regions to examine 1) how resident characteristics, facility characteristics, and state of residence explained geographic variation in opioid prescribing practices across hospital referral regions; 2) the relative strength of clustering of prescribing practices between states and hospital referral regions; and 3) the association between opioids and dose initiated. To our knowledge, this approach has never been applied to studies of geographic variation in

nursing home medication use and offered a unique look at how states may influence prescribing in comparison to healthcare markets.

For aim 3, we used a new-user, active comparator cohort study. Such a design should reduce confounding by indication and selection bias introduced by comparing incident and prevalent users ("prevalent user bias").[159,160] In comparison to prior studies of opioid safety in older adults,[58–60] we were able to incorporate a richer set of potential confounders based on the MDS 3.0. Using inverse probability of treatment weighting, we efficiently adjusted for a large number of potential confounders, which was particularly relevant given the high dimensionality of our data and the rarity of our study outcome.[161] We also conducted multiple secondary, sensitivity, and bias analyses[145,173] to examine how our results may have been affected by different analytic decisions, which provided further support for our primary study findings.

LIMITATIONS

This dissertation is not without limitations. Data are from 2011-2013, and recent laws and policy changes are likely affecting opioid prescribing in nursing homes,[174] such as the rescheduling of hydrocodone from schedule III to schedule II.[112] Additionally, aims 1 (2012 only) and 2 (2011 only; the only year that we had Part B outpatient claims available) used only one year of data. They provide no information on how the overall prevalence of long-term opioid use or geographic variation in initiation may be changing over time. Although we are skeptical that these policy changes would drastically modify the main conclusions of our work, we recognize that our results may not accurately

reflect current prescribing practices in nursing homes, which are likely shifting in response to rapidly evolving policies aimed at slowing the opioid epidemic.

Throughout, we assumed that opioids were used as prescribed. Violations of this assumption could have resulted in outcome misclassification when examining the prevalence of long-term opioid use (aim 1) or opioid initiation patterns (aim 2) if residents prescribed opioids never used their medications. If such practices were pervasive, we likely overestimated prevalent and incident opioid use. However, the majority of residents classified as long-term opioid users had documentation on the MDS 3.0 stating that they were administered analgesics (>90%; this measure is however not specific to opioids). We further doubt that the practice of filling but not using opioids is common for long-stay nursing homes residents, as these opioids cannot be easily prescribed in many states,[175] and fills likely represent efforts to alleviate acute and chronic pain and not simply as a precautionary measure for future pain. For our comparative safety study (aim 3), following persons who were prescribed but not actually using a study drug could have resulted in exposure misclassification.[176] Assuming opioids do increase the risk of fractures, this misclassification (classifying non-users as users) would have attenuated our cumulative risk estimates and biased our subdistribution hazard ratios towards or away from the null depending on the extent to which such misclassification was differential by opioid initiated.

In our work comparing the initiation and safety of commonly used opioids (aims 2-3), confounding by indication cannot be ruled out, as these medications have different

potencies and may be used differentially within nursing homes. For aim 2, if confounding by indication were present and not sufficiently adjusted for in multilevel models, we would have underestimated the extent to which resident characteristics explained variation between hospital referral region practices in opioid initiation practices. Such confounding may to some extent be present, as outpatient claims provide limited information on pain severity which may influence initiating higher doses or oxycodone.[177] However, we find it unlikely that such patterns could geographically vary to the extent needed to fully explain our results (e.g., one would have to imagine that Texas nursing home residents are so fundamentally different from all other residents as a potential reason for why they were almost never prescribed oxycodone). For aim 3, we tried to address confounding by indication with the new-user, active comparator design and a rich set of potential confounders. However, we also performed subgroup analyses and bias analyses to quantify the strength an unmeasured confounder would need to be to completely attenuate our primary results.[145,173] Alternative analytic approaches may be needed to further address confounding by indication (see **FUTURE RESEARCH DIRECTIONS**), though we believe our study design, coupled with the results from aim 2 (that resident characteristics were minimally associated with or explained patterns of geographic variation in opioid initiated) mitigate some of these concerns.

Throughout, we focused on residents who were "long-stay" and modified this definition depending on the demands of our study design including medication washout and covariate lookback periods. This study criteria requiring a study participant to reside in the same facility for 90-120 days with no recent hospitalizations or skilled nursing

facilities could introduce selection bias if our sample deviated substantially from our conceptual population of interest – older persons receiving care to manage their chronic comorbidities and/or declining functioning that is intended to be long-term.[71,178,179] Despite this, we believe our study design increased the internal validity of our results and were nonetheless worth these potential limitations.

Selection bias could have additionally been introduced by loss to follow-up (aims 1 and 3). In aim 1, we specifically looked at residents discharged from the nursing home to understand how loss to follow-up may have affected our estimates of opioid use. Although opioid use was higher in those who were lost to follow-up, accounting for these residents in our estimate of overall opioid use had minimal impact on our conclusions (32.4% vs. 33.7% overall opioid use). In our comparative safety work, we considered alternative durations of follow-up and analytic approaches that were similar to our primary findings, potentially mitigating loss to follow-up concerns.

Although the MDS 3.0 merged to Medicare claims provides data not normally available in pharmacoepidemiologic studies, we lacked information on certain confounders including end-of-life preferences and measures of terminal illness. These measures may have some impact on the types and doses of opioids used and initiated. For our work on geographic variation, these sources of unmeasured confounding may have underestimated the proportion of variation explained by resident characteristics if such preferences also geographically varied. We note that prior studies suggest that patient end-of-life care preferences have limited effect on geographic variability in end-of-life

healthcare intensity,[180] which may reduce concerns of these confounders affecting our analyses if such results extend to preferences on medications received in nursing homes. For our comparative safety work, we conducted bias analyses for unmeasured confounding, but more detailed and complete data on potential confounders would be preferable.

Previous work has raised concerns on the validity of the MDS to accurately measure resident characteristics.[181] Although this prior work focused on the MDS 2.0 and concluded that the MDS is still a suitable source of information for research, it naturally raises concerns on the quality of MDS 3.0 data. We note that recent studies suggest that the MDS 3.0 can more accurately measure resident characteristics and clinical events in comparison to previous versions of the MDS.[76,182–184] It is unclear to what extent limitations in data quality could affect this work and other studies relying on these data to study medication use and safety in nursing homes.

Acetaminophen and over-the-counter NSAIDS were not measurable with Part D claims.[185] Thus, we were limited in our abilities to describe nonopioid analgesics and could only capture prescribed NSAIDS and opioid combination products (e.g., hydrocodone/acetaminophen).Given that the primary purpose of this research was to describe opioid use and safety, we believe this limited the interpretation of our results minimally but must nonetheless be kept in mind. To our knowledge, NSAIDS and acetaminophen are not thought to increase fall of fracture risk, especially when compared to opioids.[59,60]

FUTURE RESEARCH DIRECTIONS

Our work raises a number of interesting questions for further research. As mentioned above, aims 1 and 2 used only one year of data. Given rapid changes in policy, further work to understand how the prevalence of long-term opioid use and geographic variation in opioid use are changing over time is needed. Additionally, examining how trends in the prevalence of pain may be changing in association with opioid prescribing patterns over time may provide further context and insights on the role of opioids in pain management, though such designs may be limited in their ability to disentangle the relationship between opioids and measured pain and also be limited by unmeasured confounding, measurement error, and selection bias.

Although aim 1 documented a number of opioid prescribing practices associated with overdose and death in community settings, the extent to which opioid initiation and use are associated with overdose hospitalizations and overdose-related death in nursing homes is unknown. This may be a valuable direction for future research to provide insight on the safety of using opioids in this medically supervised setting, particularly in comparison to noninstitutionalized populations. If overdose events are rare, examining naloxone prescribing may be a reasonable proxy endpoint that may conceptually capture concern and precautions against overdose, or alternatively as actual use to manage and reverse an opioid overdose.[186] This is particularly relevant given the systematic exclusion of nursing home residents from studies of overdose risk.[45–49]

Aim 2 raises questions on specific state laws and policies that may affect opioid prescribing among nursing home residents. These laws and policies (e.g., hydrocodone rescheduling)[112] could potentially relax assumptions on unmeasured confounding and represent natural experiments lending themselves to quasi-experimental approaches.[187,188] Notably, beyond just examining changes in medication use, these policy changes could be used to examine opioid effectiveness and safety if they were strong predictors of the opioid a resident is prescribed.

Our comparative safety work only examined one safety endpoint. Additional work is needed to 1) understand the comparative safety of commonly used opioids on other safety outcomes (e.g., cardiovascular disease); 2) explore the potentially mediating pathways that may explain differential risks such as fracture; and 3) extend our comparative safety work to also examine other endpoints of interest to clinicians, residents, and their families such as comparative effectiveness. Alternative treatment contrasts – such as initiating different opioid doses – also require evaluation to further understand the risk of opioids in nursing homes.

Future studies of medication use and safety in nursing homes should also consider alternative strategies to better address unmeasured confounding, measurement error, and selection bias. Such work would be responsive to calls for "triangulating" evidence in etiological epidemiology.[189,190] Triangulation refers to the process of integrating the results of several different epidemiologic approaches applied to the same causal question, with each approach having different and unrelated biases. Although our work represents a

first step in this direction by focusing on nursing home residents, who may have differing confounding structures than community-dwelling adults (i.e., a cross-cohort comparison),[191] this dissertation and the prior work by Solomon and colleagues[58] require the strong assumptions of no unmeasured confounding, measurement error, and selection bias to hold for our conclusions to be valid. In the spirit of triangulation, future studies addressing this study question could apply alternative analytic approaches that have different, unrelated biases including natural experiments (e.g., state policy changes, highlighted above),[187] instrumental variables,[192,193] and negative control exposures and/or outcomes.[194,195] Adapting these approaches could provide further context for the comparative safety of commonly used opioids and fracture hospitalizations and are particularly relevant given how underrepresented nursing home residents are in clinical research.

APPENDICES FOR CHAPTER II

Appendix 2.1: Specific opioid medications prescribed to study participants during the 120 day follow-up window (N=315,949).

Medication Used (%)[1]	Overall (N=315,949)	Any opioid use (n=102,297)	Stratified by length of opioid use		
			Short-term (n=31,252)	Medium-term (n=19,724)	Long-term (n=46,744)
Any Opioid	32.4				
Short-acting opioids[2]	30.3	93.5	99.4	98.2	87.5
Codeine / acetaminophen	1.1	3.3	4.9	3.0	2.4
Hydrocodone / acetaminophen	16.9	52.5	53.7	59.8	48.9
Hydrocodone / NSAID	0.0	0.1	0.1	0.1	0.2
Hydromorphone	0.2	0.7	0.3	0.8	0.8
Morphine	0.7	2.1	2.7	1.9	1.9
Oxycodone	1.4	4.3	2.9	4.7	5.0
Oxycodone / acetaminophen	2.5	7.8	6.8	8.9	8.0
Tramadol	9.9	30.4	31.3	29.1	30.4
Tramadol / acetaminophen	0.5	1.5	1.4	1.5	1.6
Long-acting opioids[3]	5.8	17.8	1.0	5.5	34.3
Buprenorphine	0.0	0.1	0.0	0.1	0.2
Fentanyl	4.0	12.5	0.7	3.4	23.9
Methadone	0.3	1.0	0.1	0.4	1.9
Morphine extended release	0.9	2.7	0.1	0.8	5.3
Oxycodone extended release	0.6	1.9	0.1	0.8	3.6
Tramadol extended release	0.0	0.1	0.1	0.1	0.2

[1]Columns do not add up to 100% because some participants received more than one type of opioid.
[2]Short-acting opioids (single-agents and/or combinations) used by <0.1% of all opioid users were not presented but include: codeine (as a single agent), dihydrocodeine, meperidine, nalbuphine, oxycodone/NSAID, oxymorphone, pentazocine, and tapentadol.
[3]Long-acting opioids used by <0.1% of all opioid users were not presented but include: butorphanol, hydromorphone extended release, oxymorphone extended release, and tapentadol extended release.

Appendix 2.2: Specific NSAIDS, pain adjuvants, and other medications used for pain and prescribed to study participants (overall and stratified by any opioid use and length of opioid use) during the 120 day follow-up window. (N=315,949).

		Stratified by any opioid use		Stratified by length of opioid use		
Medication Used (%)[1]	**Overall (N=315,949)**	**No use (n=213,652)**	**Any use (n=102,297)**	**Short-term (n=32,841)**	**Medium-term (n=20,615)**	**Long-term (n=48,841)**
NSAID prescriptions[2]	10.9	8.4	16.1	15.3	17.5	16.0
Celecoxib	1.5	1.0	2.4	2.0	2.7	2.5
Diclofenac	1.9	1.1	3.6	2.8	3.9	4.0
Etodolac	0.1	0.1	0.2	0.1	0.2	0.2
Ibuprofen	2.6	2.3	3.0	3.5	3.0	2.7
Indomethacin	0.2	0.2	0.3	0.4	0.3	0.3
Ketorolac	0.1	0.0	0.2	0.1	0.2	0.2
Meloxicam	3.6	2.6	5.6	5.4	6.5	5.4
Nabumetone	0.3	0.3	0.5	0.4	0.4	0.5
Naproxen	1.3	1.1	1.8	1.9	1.9	1.6
Sulindac	0.1	0.1	0.1	0.1	0.1	0.1
Pain Adjuvants	20.7	14.9	32.9	27.6	34.7	35.7
Anticonvulsants	14.2	9.7	23.6	19.7	25.5	25.4
Carbamazepine	1.2	1.2	1.3	1.4	1.1	1.3
Gabapentin	10.9	7.0	19.0	15.5	20.8	20.5
Lamotrigine	1.1	1.0	1.2	1.2	1.3	1.2
Pregabalin	1.7	0.9	3.4	2.7	3.7	3.8
Antidepressants[3]	9.2	6.4	15.0	11.6	15.6	17.1
Tricyclics[4]	1.4	1.0	2.4	1.8	2.5	2.7
Amitriptyline	0.9	0.6	1.6	1.2	1.8	1.8
Nortriptyline	0.5	0.4	0.8	0.6	0.7	0.9
SNRIs [5]	8.0	5.5	13.0	10.0	13.4	14.9
Duloxetine	4.8	2.8	9.1	6.4	9.6	10.7
Venlafaxine	3.2	2.8	4.1	3.7	4.0	4.3
Other medications used for pain	15.7	11.0	25.5	21.8	27.4	27.2
Corticosteroids[6]	8.3	6.4	12.1	11.2	13.1	12.2
Dexamethasone	0.4	0.3	0.7	0.7	0.8	0.7
Prednisone	6.4	5.0	9.2	8.4	9.9	9.4
Methylprednisolone	2.1	1.6	3.1	3.1	3.4	2.9
Muscle relaxants[7]	4.6	2.7	8.5	6.6	9.1	9.6
Baclofen	2.2	1.6	3.6	2.8	3.5	4.1

Carisoprodol	0.2	0.1	0.4	0.2	0.4	0.4
Cyclobenzaprine	1.5	0.7	3.2	2.6	3.7	3.5
Metaxolone	0.1	0.1	0.2	0.2	0.2	0.2
Methocarbamol	0.4	0.2	0.9	0.7	0.9	1.0
Tizanidine	0.6	0.3	1.2	0.8	1.3	1.4
Transdermal lidocaine	4.3	2.4	8.4	6.2	9.2	9.5
Potentially contraindicated psychopharmacologics[8]						
Antipsychotics	26.3	26.9	25.1	25.1	25.7	24.8
Anxiolytics	19.0	15.4	26.7	23.0	29.7	27.9
Hypnotics	4.8	3.1	8.4	7.3	10.1	8.5

Abbreviations: NSAID: nonsteroidal anti-inflammatory drug ;SNRI: serotonin-norepinephrine reuptake inhibitor

[1]Columns do not add up to 100% because some participants received more than one type of opioid.

[2]NSAIDS prescribed to <0.1% of the total population were not presented but include: choline magnesium salicylate, diflunisal, fenoprofen, flurbiprofen, ketoprofen, oxaprozin, piroxicam, salsalate, and tolmetin

[3]Limited to antidepressants commonly used as pain adjuvants as defined in the 2009 American Geriatrics Society persistent pain guidelines.[23]

[4]Tricyclics used by <0.1% of the total population were not presented but include: desipramine

[5]SNRIs used by <0.1% of the total population were not presented but include: milnacipran

[6]Corticosteroids used by <0.1% of the total population were not presented but include: prednisolone

[7]Muscle relaxants used by <0.1% of the total population were not presented but include: chlorzoxazone, dantrolene, orphenadrine

[8]Defined using the Minimum Data Set during 120-day follow-up (excludes the index MDS assessment).

Appendix 2.3: Association between resident characteristics and long-term opioid use, restricted to residents in persistent pain (n=48,922)

Characteristic	Long-term opioid use, %	Crude PR (95% CI)	Adjusted PR[1] (95% CI)
Age, years			
65-74	37.7	Referent	Referent
75-84	36.7	0.97 (0.94–1.00)	0.98 (0.95–1.01)
≥85	34.1	0.91 (0.88–0.94)	0.90 (0.87–0.93)
Gender			
Men	31.8	Referent	Referent
Women	36.5	1.14 (1.10–1.18)	1.09 (1.05–1.12)
Race/ethnicity			
Non-Hispanic White	36.6	Referent	Referent
Non-Hispanic Black	29.8	0.82 (0.78–0.86)	0.88 (0.84–0.93)
Hispanic/Latino	28.4	0.79 (0.73–0.85)	0.87 (0.80–0.95)
Asian	22.6	0.65 (0.52–0.79)	0.71 (0.57–0.80)
Other	28.6	0.80 (0.66–0.96)	0.82 (0.68–0.98)
Cognitive Impairment			
No/mild	38.7	Referent	Referent
Moderate	34.1	0.89 (0.86–0.91)	0.92 (0.89–0.95)
Severe	31.1	0.81 (0.78–0.83)	0.86 (0.83–0.89)
Physical impairment			
No/mild	36.8	Referent	Referent
Moderate	34.6	0.94 (0.91–0.96)	0.97 (0.95–1.00)
Severe	36.5	1.00 (0.97–1.03)	1.07 (1.03–1.11)

Abbreviations: CI: confidence interval; PR: prevalence ratio

[1]Prevalence ratios were estimated using modified Poisson models (using generalized estimating equations to account for clustering within nursing homes).[91] Models are adjusted for all resident characteristics in Table 1 and state of residence.

APPENDICES FOR CHAPTER III

Appendix 3.1: Study and non-study opioids and OME conversion factors

Opioid	OME conversion factor (study drugs only)[1]
Study opioids (short-acting, oral formulations only)	
Hydrocodone (hydrocodone/acetaminophen, hydrocodone/NSAID)[2]	1.0
Oxycodone (oxycodone, oxycodone/acetaminophen, oxycodone/NSAID)	1.5
Tramadol (tramadol, tramadol/acetaminophen)	0.1
Non-study opioids (including both short- and long-acting formulations when applicable; also includes oral, injection, transdermal, and other formulations [e.g., nasal] when applicable)	
Buprenorphine	-
Butorphanol	-
Codeine	-
Dihydrocodeine	-
Fentanyl	-
Hydromorphone	-
Levorphanol	-
Meperidine	-
Methadone	-
Morphine	-
Nalbuphine	-
Oxycodone, parenteral	-
Oxymorphone	-
Pentazocine	-
Tapentadol	-

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; OME, oral morphine equivalent

[1]Based on Center for Disease Control and Prevention recommendations.[101]

[2]excludes cough preparations

Appendix 3.2: International Classification of Disease, Ninth Revision, Clinical Modification codes used to define painful comorbidities reported on Medicare Part B claims[1]

Comorbidity	Definition
Injuries (excludes poisonings)	
Fracture	733.1x, 800.xx - 829.xx
Dislocations	830.xx – 839.x
Sprains	840.xx-848.xx
Intracranial injury	850.xx-854.xx
Internal injury of thorax, abdomen, pelvis	860.xx-869.xx
Open wounds	870.xx-897.xx
Blood vessel injuries	900.xx-904.xx
Superficial injuries	910.xx-919.xx
Contusions	920.xx-924.xx
Crushing injury	925.xx-929.xx
Foreign body entering through orifice	930.xx-939.xx
Burns	940.xx-949.xx
Traumatic complications / unspecified	958.xx-959.xx
External cause of injury	E800.x–E849.x; E880.x–E909.x; E916.x–E928.x; E953.x–E968.x; E970.x–E976.x; E983.x–E999.x
Chronic pain	338.0, 338.2x, 338.4, 780.96
Abdominal pain	789.0x
Musculoskeletal pain	
Back/neck pain	720.xx-224.xx
Limb pain	354.4, 355.71, 729.5
Arthritis/rheumatism/joint pain/myalgia	710.xx-719.xx, 725.xx-729.xx (excluding 729.5)
Neuropathic pain	53.1x, 250.6x, 336.9, 337.1, 337.2x, 340, 341.9, 350.x, 351.x, 353.x, 354.x, 355.x, 356.x, 357.81, 729.2, 951.4, 952.xx, 953.4, 955.5, 955.6, 955.7

[1]Diagnoses were primarily defined using Davis et al., 2011;[196] Caplan et al., 2010;[197] Narayana et al., 2015;[198] and Mack et al., 2015.[199]

Appendix 3.3: Complete resident and facility characteristics of long-stay residents initiating opioids in 2011, overall and stratified by opioid and dosage strength initiated (N=62,889 residents in 12,345 facilities within 298 hospital referral regions).

		Stratified by opioid initiated			Stratified by dose initiated / day	
Characteristic[1], %	**Overall (N=62,889)**	**Oxycodone (n=5,891)**	**Hydrocodone (n=35,326)**	**Tramadol (n=21,672)**	**≥50 mg OME (n=4,232)**	**<50 mg OME (n=58,657)**
Resident characteristics						
Age, years						
65-74	15.9	19.1	17.2	12.9	22.0	15.4
75-84	31.2	32.3	31.7	29.9	34.1	30.9
≥85	53.0	48.6	51.1	57.2	44.0	53.6
Women	75.8	73.0	74.3	79.1	69.9	76.2
Race/ethnicity						
Non-Hispanic white	82.3	80.3	82.1	83.2	82.2	82.3
Non-Hispanic black	11.7	13.7	11.7	11.1	11.8	11.7
Hispanic/Latino	4.5	4.6	4.5	4.6	4.7	4.5
Other	1.5	1.4	1.7	1.1	1.3	1.5
Physical limitations[2]						
None/mild	27.8	21.8	27.6	29.7	26.5	27.8
Moderate	50.7	52.9	50.5	50.4	54.1	50.5
Severe	21.5	25.3	21.9	20.0	19.4	21.7
Cognitive impairment[3]						
None	29.0	34.1	27.9	29.3	32.0	28.8
Moderate	31.5	31.5	31.5	31.5	32.6	31.4
Severe	39.5	34.4	40.6	39.2	35.4	39.8
Dementia	59.4	53.9	59.4	60.7	53.9	59.8
Psychopharmacologic Medications[4]						
Antidepressants	62.3	64.9	63.1	60.4	64.2	62.2
Antipsychotic	27.5	24.5	28.3	26.9	26.5	27.5
Antianxiety	21.3	20.5	22.0	20.4	19.4	21.4
Hypnotics	6.5	6.7	6.7	6.1	7.2	6.4
Other medications prescribed for pain[4]						
Anticonvulsants	15.5	19.5	15.7	13.9	18.4	15.2
Corticosteroids	7.2	7.8	7.1	7.1	7.3	7.2
Muscle relaxants	4.1	5.1	4.3	3.6	5.7	4.0
NSAIDS	11.6	10.7	11.2	12.6	10.8	11.7
Pain recorded on MDS[5]						
None	66.9	62.0	66.9	68.3	63.3	67.2
Any self-reported pain	28.8	33.4	28.6	28.0	33.0	28.5
Any staff-assessed pain	4.2	4.6	4.5	3.6	3.7	4.3

Painful comorbidities[5,6]						
Any injury (excludes poisonings)	18.3	22.6	19.0	15.8	21.2	18.0
Pressure ulcers	7.4	11.3	7.2	6.5	8.8	7.3
Diagnosed chronic pain	2.7	4.0	2.5	2.6	3.3	2.7
Abdominal pain	5.5	7.2	5.2	5.3	6.5	5.4
Musculoskeletal pain	64.0	67.5	62.6	65.4	62.2	64.1
Neuropathic pain	7.3	8.2	7.3	6.9	9.1	7.1
Any emergency room use	16.2	18.0	17.7	13.3	18.8	16.0
Total number of Part B claims						
<5	21.9	14.0	22.1	23.7	18.7	22.1
5-9	33.2	28.4	33.4	34.1	29.2	33.5
10-14	20.3	22.5	20.3	19.6	21.1	20.2
≥15	24.7	35.1	24.2	22.6	31.0	24.2
Facility characteristics						
Rural location	31.6	19.1	33.6	31.9	28.0	31.9
Size, number of beds						
<100	30.5	22.2	32.5	29.4	29.6	30.5
100-199	58.6	56.5	58.2	59.6	60.7	58.4
≥200	11.0	21.3	9.3	11.0	9.7	11.1
Ownership						
For profit	73.1	68.2	75.0	71.3	77.3	72.8
Government	5.7	6.0	5.3	6.1	4.3	5.8
Non profit	21.3	25.8	19.7	22.6	18.3	21.5
Part of a chain	57.6	49.6	59.1	57.3	61.7	57.3
Occupancy, %						
<80	26.4	16.0	28.4	25.9	29.2	26.2
80-89	29.8	28.2	30.1	29.8	30.2	29.8
90-94	23.3	27.3	22.5	23.3	22.7	23.3
≥95	20.5	28.5	18.9	20.9	17.9	20.7
Residents in facility receiving skilled nursing care, %						
<10	35.6	34.3	37.1	35.6	33.3	36.6
10-19	46.5	46.6	46.2	47.0	47.0	46.5
≥20	17.1	19.1	16.7	17.3	19.7	16.9
Nursing home compare quality rating, stars						
1	9.4	8.0	10.0	8.7	10.4	9.3
2	19.0	17.4	19.1	19.0	18.9	19.0
3	25.6	25.5	25.4	26.0	25.6	25.6

4	32.2	33.6	31.8	32.5	33.0	32.2
5	13.9	15.4	13.7	13.7	12.1	14.0
Residents with facility-acquired bed sores, %						
0	15.7	13.2	15.7	16.4	15.0	15.8
0.1-2.4	34.6	37.8	34.2	34.4	35.8	34.5
2.5-4.9	30.5	31.6	30.4	30.3	30.6	30.5
≥5%	19.2	17.4	19.7	18.8	18.5	19.2
Residents restrained, %						
0	38.9	37.3	38.3	40.4	41.6	38.7
0.1-1.9	18.8	22.5	18.1	19.0	18.1	18.9
2.0-4.9	21.7	20.5	22.0	21.6	20.6	21.8
≥5	20.5	19.8	21.6	19.1	19.7	20.6
Registered nurse staffing, minutes per resident day						
<27.3	27.9	17.2	30.1	28.1	26.5	28.0
27.4-36.8	26.7	25.3	27.3	26.4	25.7	26.7
36.9-48.3	24.5	29.9	23.5	25.2	24.6	24.5
≥48.4	21.0	27.5	19.1	20.3	23.3	20.8
Physician staffing, minutes per resident day						
<0.3	25.9	20.1	26.5	26.4	24.1	26.0
0.3-0.6	26.4	24.0	26.9	26.8	27.6	26.4
0.7 -1.1	24.5	25.9	24.5	24.5	25.5	24.5
≥1.2	23.2	30.0	22.1	22.3	22.8	23.2
Physician extender staffing, minutes per resident day						
0	57.5	51.5	58.6	57.3	55.6	57.6
0.1-0.6	16.6	14.9	16.7	16.9	16.3	16.6
≥0.7	25.9	33.7	24.8	25.7	28.1	25.8

Abbreviations: MDS, Minimum Data Set; NSAIDS, nonsteroidal anti-inflammatory drugs; OME, oral morphine equivalents

[1]Column percentages may not add to 100% due to rounding.

[2]Physical limitations were defined using the Activities of Daily Living Self-Performance Hierarchy (range: 0-6) to categorize residents as having no/mild (0-2), moderate (3-4), or severe limitations (5-6).

[3]Cognitive impairment was defined using the Brief Interview for Mental Status (BIMS; range: 0-15) when the resident could self-report and the Cognitive Performance Scale (CPS; range: 0-6) otherwise: none/mild (BIMS 13-15 or CPS 0-2), moderate (BIMS 8-12 or CPS 3-4) or severe impairment (BIMS 0-7 or CPS 5-6).

[4]Subcategories are not mutually exclusive and may add to >100%.

[5]Derived from the most recent Minimum Data Set assessment preceding opioid initiation.

[6]Based on Part B claims from the 90 days prior to opioid initiation (see Appendix 3.2 for further information on definitions used). The total number of Part B claims (median and interquartile range [IQR]) varied by opioid initiated: hydrocodone (8, IQR: 5-14), oxycodone (11, IQR: 6-18), tramadol (8, IQR: 5-13).

Appendix 3.4: Further details on multilevel modelling.

Overview. We were interested in quantifying geographic variation in opioid prescribing practices to examine 1) the extent to which variation in opioid prescribing between hospital referral regions (HRR) could be explained by differences in resident characteristics, facility characteristics, and state of residence; and 2) the correlation in the propensity of persons within similar geographic areas – including HRRs and state of residence – to initiate similar opioids or doses. To accomplish these aims, we fit a series of multilevel logistic models to explicitly model geographic variation with random intercepts and progressively adjusting for resident characteristics, facility characteristics, and state.[105,200,201]

Outcomes. Opioid prescribing practices of interest included initiating specific commonly-used opioids (e.g., initiating hydrocodone vs. initiating oxycodone or tramadol) or doses ≥50 mg oral morphine equivalents (OME) per day versus doses <50 mg OME/day. Outcomes were dichotomized to enhance clinical interpretability and because we were conceptually interested in measuring the variation of particular prescribing practices versus all other common practices and not with respect to a specific referent medication (i.e., as one would estimate with a multinomial model).

Model Building. For each outcome, we sequentially fit a series of 4 models that progressively adjusted for resident characteristics, facility characteristics, and state of residence while measuring the variance parameters of interest. Models were sequentially fit so that we could examine the extent to which differences in resident characteristics,

facility characteristics, and state contributed to any observed geographic variation between HRRs. The models included:

Model 1. Null multilevel logistic model including random intercepts for HRRs:

$$\text{logit}\left(P\left(Y_{ij}=1\middle|\alpha_{oj}\right)\right)=\beta_0+\alpha_{0j}, \quad (1)$$

where the outcome Y_{ij}=1 if resident i within HRR j initiated the study opioid or dose of interest and Y_{ij}=0 otherwise, β_0 is the log-odds of the proportion of initiators initiating the study opioid or dose at the average HRR, and α_{0j} is the HRR-specific random intercept measuring variation in the proportion of initiators prescribed specific opioids or dose on the logistic scale, assumed to be normally distributed with mean 0 and variance ${\sigma_{HRR}}^2$, $\alpha_{0j}\sim N(0,\sigma_{HRR}^2)$. The variance of the random intercepts for HRRs (${\sigma_{HRR}}^2$) from model 1 provide a crude (unadjusted) estimate of between-HRR variation on the logistic scale.

Model 2. Multilevel logistic model adjusting for resident characteristics and including random intercepts for HRRs:

$$\text{logit}\left(P\left(Y_{ij}=1\middle|\alpha_{oj},\boldsymbol{X}_{ij}^{r}\right)\right)=\beta_0+\boldsymbol{\beta_{res}}\boldsymbol{X_{ij}^{r}}+\alpha_{0j}, \quad (2)$$

where Y_{ij}, β_0 , α_{0j} are as described in equation 1 but we additionally adjusted for a vector of resident characteristics $\boldsymbol{X}_{ij}^{r}$ included in the model as fixed effects (see Appendix 3.3 for specific resident characteristics included). The variance of the random intercepts for HRRs (${\sigma_{HRR}}^2$) from model 2 estimates between-HRR variation on the logistic scale after adjusting for measured resident characteristics.

Model 3. Multilevel logistic model adjusting for resident and facility characteristics and including random intercepts for HRRs:

$$\text{logit}\left(P\left(Y_{ij}=1\middle|\alpha_{oj},\boldsymbol{X}_{ij}^{r},\boldsymbol{X}_{ij}^{f}\right)\right)=\beta_0+\boldsymbol{\beta_{res}}\boldsymbol{X}_{ij}^{r}+\boldsymbol{\beta_{fac}}\boldsymbol{X}_{ij}^{f}+\alpha_{0j}, \quad (3)$$

with all previously defined variables in equations 1-2 and additionally adjusted for a vector of facility characteristics $\boldsymbol{X}_{ij}^{f}$ included as fixed effects (see Appendix 3.3). Note that because most facilities included few study participants, we did not adjust for clustering within facilities using random intercepts due to concerns of increasing bias when estimating variance components.[202] The variance of the random intercepts for HRRs from model 3 provides an adjusted estimate of between-HRR variation on the logistic scale after accounting for measured resident and facility characteristics.

Model 4. Cross-classified logistic model adjusting for resident and facility characteristics and including random intercepts for HRRs and state:

$$\text{logit}\left(P\left(Y_{ijk}=1\middle|\alpha_{oj},\alpha_{0k},\boldsymbol{X}_{ijk}^{r},\boldsymbol{X}_{ijk}^{f}\right)\right)=\beta_0+\boldsymbol{\beta_{res}}\boldsymbol{X}_{ijk}^{r}+\boldsymbol{\beta_{fac}}\boldsymbol{X}_{ijk}^{f}+\alpha_{0j}+\alpha_{0k}, \quad (4)$$

with all previously described variables (equations 1-3, but with a subscript for state k added to the vectors of resident and facility characteristics) and an additional random intercept for state of residence with mean 0 and variance σ_{State}^2, $\alpha_{0k}\sim N(0,\sigma_{State}^2)$ to separately estimate the contributions of state and HRRs to variation in opioid prescribing. Cross-classified models were used to account for the non-nested data structure (see Figure 1). This model was used to 1) estimate the between-HRR variation adjusted for resident and facility characteristics and state of residence (random effect α_{0k}); 2) separately compare clustering within states and within HRRs, as defined below.

Measuring proportional change in between HRR variation. To achieve our aim to understand the extent that between-HRR variation of initiating specific opioids or doses could be explained by resident characteristics, facility characteristics, and state of residence, we estimated the proportional change in between-HRR variation (PCV). The PCV is a percentage reflecting the between-HRR variation explained by the multilevel model and is defined separately for models 2-4 in reference to model 1 as:

$$\frac{\hat{\sigma}_{HRR}{}^{2}{}_{(model\ 1)} - \hat{\sigma}_{HRR}{}^{2}{}_{(model\ x)}}{\hat{\sigma}_{HRR}{}^{2}{}_{(model\ 1)}} \times 100, \quad (5)$$

where $\hat{\sigma}_{HRR}{}^{2}{}_{(model\ 1)}$ is the estimated variance of the random intercepts for HRRs from model 1 and $\hat{\sigma}_{HRR}{}^{2}{}_{(model\ x)}$ is the estimated variance of the random intercepts for HRRs from any model 2-4. The PCV can increase or decrease (i.e., negative percentages because adding covariates increased the variance of the distribution of the random effects for HRRs)[105,116] with the addition of resident and facility characteristics.

Measuring the strength of clustering within HRRs versus within states. To understand clustering of opioid prescribing practices within similar geographic areas, we estimated intraclass correlation coefficients (ICC) for models 1-4. The ICC measures the correlation in the propensity to either initiate the same opioid or similar doses among two persons chosen at random from the same geographic area. As the ICC increases from 0 to 1, it indicates that residents within the same area are more likely to be prescribed the same opioid (i.e., they are more similar to each other, and conversely more different from persons in other areas). The ICC was estimated using the latent response formulation of the logistic model. For models 1-3, we estimated the ICC within HRRs (ICC_{HRR}) as:

$$ICC_{HRR(model\ x)} = \frac{\hat{\sigma}_{HRR}{}^{2}{}_{(model\ x)}}{\hat{\sigma}_{HRR}{}^{2}{}_{(model\ x)} + \frac{\pi^2}{3}}, \quad (6)$$

In which $\hat{\sigma}_{HRR}{}^{2}{}_{(model\ x)}$ is the estimated variance of the random intercepts for HRRs for models 1-3 and $\frac{\pi^2}{3}$ represents the between-resident variance, which is held constant across multilevel logistic models.[105,201] For cross-classified models (model 4), we estimated ICC_{HRR} after partitioning out state variation (i.e., examining the ICC between persons in the same HRR but different states) as:

$$ICC_{HRR(model\ 4)} = \frac{\hat{\sigma}_{HRR}{}^{2}{}_{(model\ 4)}}{\hat{\sigma}_{HRR}{}^{2}{}_{(model\ 4)} + \hat{\sigma}_{State}{}^{2}{}_{(model\ 4)} + \frac{\pi^2}{3}}, \quad (6)$$

where $\hat{\sigma}_{HRR}{}^{2}{}_{(model\ 4)}$ is the estimated variance of the random intercepts for HRRs, $\hat{\sigma}_{State}{}^{2}{}_{(model\ 4)}$ is the estimated variance of the random intercepts for states, and $\frac{\pi^2}{3}$ is between-resident variance. For model 4, we additionally estimated the ICC within states after partitioning out HRR variation (ICC_{state}; examines the ICC between persons in the same state but different HRRs) as:

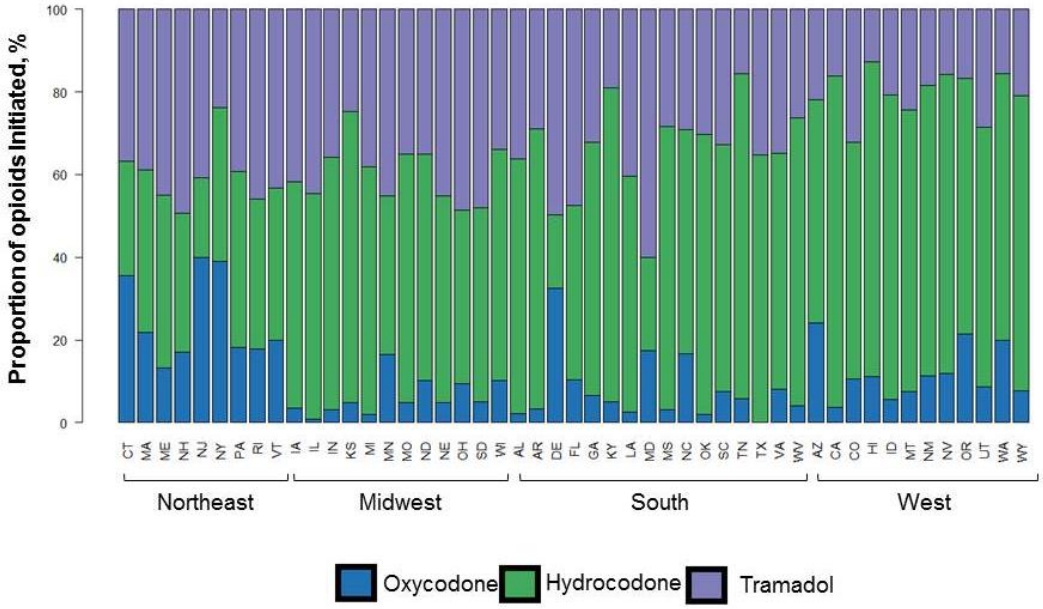
$$ICC_{State(model\ 4)} = \frac{\hat{\sigma}_{State}{}^{2}{}_{(model\ 4)}}{\hat{\sigma}_{HRR}{}^{2}{}_{(model\ 4)} + \hat{\sigma}_{State}{}^{2}{}_{(model\ 4)} + \frac{\pi^2}{3}}, \quad (7)$$

with all parameters previously defined in equation 6.

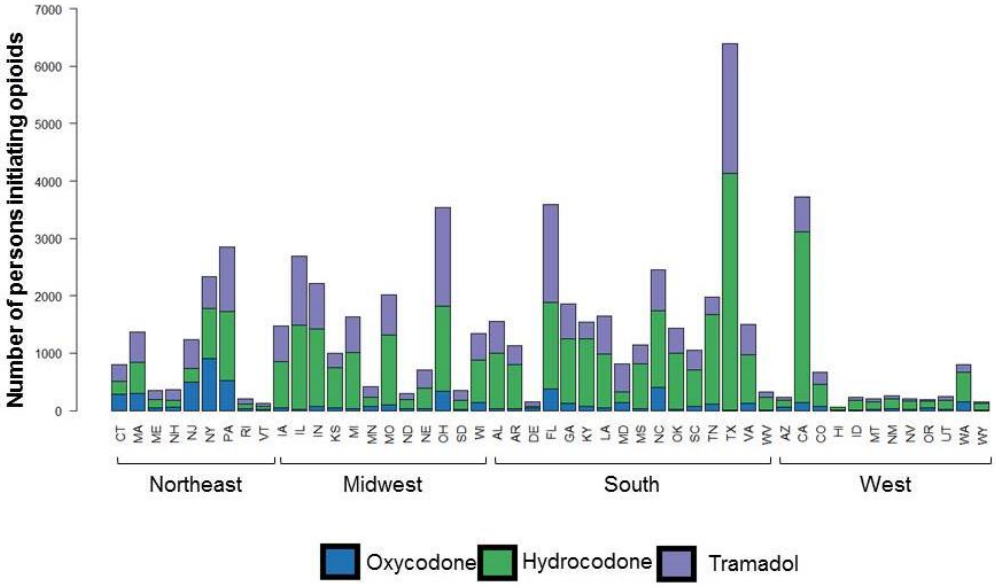
Statistical Software. All multilevel logistic models were estimated with 'proc glimmix' and the Laplace method using SAS 9.4 (SAS Institute, Cary, NC, USA).

Appendix 3.5: Summary of the proportion and absolute number of residents initiating oxycodone, hydrocodone, tramadol, or doses ≥50 mg OME/day by state (N=62,889)

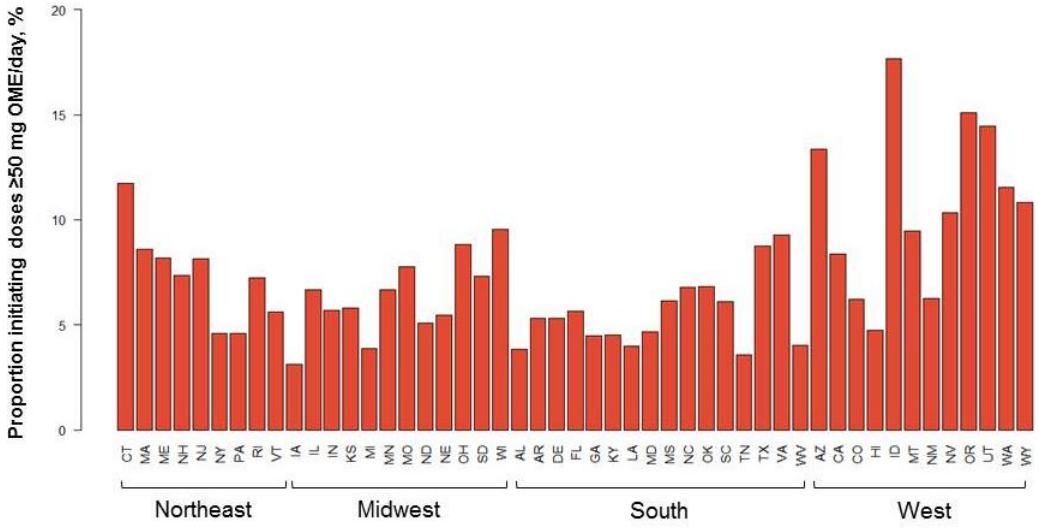
Proportion of residents initiating opioids that were prescribed short-acting formulations of oxycodone, hydrocodone, or tramadol by state.



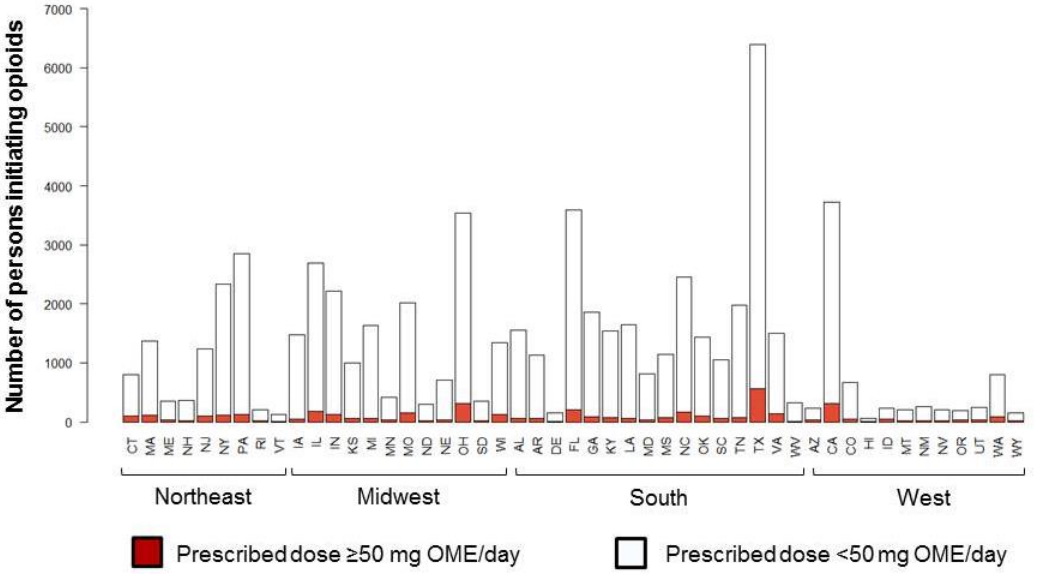
Absolute number of residents initiating oxycodone, hydrocodone, or tramadol by state.



Proportion of residents initiating opioids that were prescribed doses ≥50 mg OME/day by state.



Absolute number of long-stay residents initiating opioids and prescribed ≥50 mg OME/day by state.



Appendix 3.6: Model variance components; measures of between-HRR variation explained by resident characteristics, facility characteristics, and state; and the magnitude of clustering within geographic areas for commonly initiated opioids and initiating doses ≥50 mg OME/day (N=62,889 residents in 12,345 facilities within 298 hospital referral regions).

	Characteristics included in multilevel model[1]			
	Null model	**Resident**	**Resident + Facility**	**Resident + Facility + State**
Initiating oxycodone				
τ^2 for HRR	1.8972	1.8718	1.7491	0.3024
τ^2 for state	-	-	-	1.1415
PCV[2]	Referent	1.3%	7.8%	84.1%
ICC_{HRR}[3]	0.37	0.36	0.35	0.06
ICC_{state}[3]	-	-	-	0.24
Initiating hydrocodone[4]				
τ^2 for HRR	0.6400	0.6529	0.6391	0.2676
τ^2 for state	-	-	-	0.3395
PCV	Referent	-2.0%	1.4%	58.2%
ICC_{HRR}	0.16	0.17	0.16	0.07
ICC_{state}	-	-	-	0.09
Initiating tramadol[4]				
τ^2 for HRR	0.3585	0.3721	0.3673	0.1466
τ^2 for state	-	-	-	0.2116
PCV	Referent	-3.8%	-2.4%	59.1%
ICC_{HRR}	0.10	0.10	0.10	0.04
ICC_{state}	-	-	-	0.09
Initiating doses ≥50 mg OME/day				
τ^2 for HRR	0.2256	0.2288	0.2061	0.1211
τ^2 for state	-	-	-	0.09463
PCV	Referent	-1.4%	8.6%	46.3%
ICC_{HRR}	0.06	0.07	0.06	0.03
ICC_{state}	-	-	-	0.03

Abbreviations: τ^2, variance of the random intercept; HRR, hospital referral region, ICC, intraclass correlation coefficient; OME, oral morphine equivalent; PCV, proportional change in between hospital referral region variation explained by the model

[1]Multilevel logistic models with a random intercept for hospital referral region were sequentially fitted using resident and facility characteristics listed in Appendix 3.3. The final model was a cross-classified multilevel model including a second random intercept for state.

[2]PCV describes the proportional change in HRR variation explained by the multilevel model and was estimated as (variance of random intercept in null model – variance of random intercept in adjusted model) / variance of random intercept in null model.

[3]ICC estimates the correlation between two individuals randomly selected from each HRR and was estimated based on the latent response formulation of the multilevel logistic model.[105] The cross-classified model was used to estimate the correlation between two persons in the same HRR but different states (ICC_{HRR}) and the same states but different HRRs (ICC_{state}).

[4]Adding resident and facility characteristics to this model increased the variance. This can occur when there is negative correlation between the opioid initiated and resident factors within HRRs.[116]

APPENDICES FOR CHAPTER IV

Appendix 4.1:

Data sources used in this study included the Minimum Data Set 3.0 merged to the Medicare enrollment (Master Beneficiary Summary File), pharmacy (Medicare Part D), and hospitalization files (Medicare Part A). Resident data were linked using a unique encrypted beneficiary identifier.

The cohort included residents newly initiating short-acting oral formulations of hydrocodone, oxycodone, or tramadol during the period of 05/01/2011 to 12/31/2013. Residents had to meet all inclusion/exclusion criteria on the day the prescription was filled. The number of eligible participants and final number of initiation episodes are shown in **Table 4.1**; see **Figure 4.1** for an overview of the study design.

Criterion 1 and 2 limited the study population to Medicare-eligible long-stay nursing home residents, defined as residents with >120 day stay in the same nursing home facility with 4 months of Medicare Part A, Part B, and Part D coverage. We excluded residents with Part C (Medicare Advantage) coverage because their claims may be incomplete. We included only long-stay nursing home residents because they require long-term assistance to manage chronic disabilities and are different from short-stay residents.[71] Although many prior studies of nursing home residents define "long-stays" using shorter time periods (e.g. ≥90 days or >100 days),[71,133,203,204] we used a more conservative definition to ensure that we had a 4-month washout period (for defining new use) and to assess covariates.

Criterion 3 limited the sample to new episodes of initiating oral formulations of short-acting hydrocodone, oxycodone, or tramadol.[159] Long-acting formulations were excluded. Residents prescribed multiple study drugs on the index date were not included.

Criterion 4 excluded initiation episodes that were preceded by any SNF care or hospitalizations in the prior 120 days because these services – including medications used in this period – are paid for by Medicare Part A and represent 'immeasurable time'[205] when we could not assess medication use with Part D claims.

Criterion 5 restricted the sample to episodes with any MDS 3.0 assessment (quarterly or comprehensive) in prior 120 days AND a comprehensive assessment in the prior 365 days. Quarterly assessments are condensed and do not collect information on many chronic comorbidities (e.g., cancer, arthritis, osteoporosis). Therefore, we used prior comprehensive assessments to assess medical comorbidities that were not recorded on the condensed quarterly assessments.

Criterion 6 excluded episodes of care in provider-based facilities or free-standing SNFs because these facilities provide more extensive services and primarily serve different patient populations.[206]

Criterion 7 excluded residents <65 years because we were primarily interested in older residents who may be clinically different from younger Medicare beneficiaries (e.g., they may be covered because they are disabled). Criterion 8-9 excluded those with cancer or receiving hospice care because pain management guidelines are different for these populations. Criterion 10 excluded comatose residents. Criterion 11 excluded residents with any missing data.

Criterion 12 excluded treatment episodes with unusually high starting doses (>180 mg oral morphine equivalents).[124,125]

Criterion 13 excluded residents from states/districts contributing <100 treatment episodes to the analysis (Alaska, Washington DC). Criterion 14 excluded residents from states where <2% of treatment episodes were oxycodone (Illinois, Michigan, Texas). We implemented these criteria to increase covariate balance between treatment groups.

Unique residents could contribute multiple opioid initiation episodes if they met eligibility criteria.

Appendix 4.2: Study and non-study opioids

Study opioids and oral morphine equivalent (OME) conversion factors.[101]

Drug[1,2]	OME Conversion Factor[3]
Hydrocodone (hydrocodone/acetaminophen, hydrocodone/NSAID)[4]	1.0
Oxycodone (oxycodone, oxycodone/acetaminophen, oxycodone/NSAID)	1.5
Tramadol (tramadol, tramadol/acetaminophen)	0.1

[1]We combined single agent and combination products (e.g., tramadol included both tramadol only tablets and tramadol/acetaminophen combination products).
[2]Does not include parenteral formulations. Only short-acting formulations were included.
[3]Conversion factors are to convert from mg/day of study drug to mg/day of oral morphine
[4]Does not include hydrocodone in cough preparations.

Non-study opioids[1,2]

Buprenorphine
Butorphanol
Codeine
Dihydrocodeine
Fentanyl
Hydromorphone
Levorphanol
Meperidine
Methadone
Morphine
Nalbuphine
Oxycodone, parenteral
Oxymorphone
Pentazocine
Propoxyphene
Tapentadol

[1]Non-study drug could not be prescribed in the washout period and were censoring events when prescribed during follow-up
[2]Includes both short- and long-acting formulations when applicable. Formulations considered included oral, injection, transdermal, and other less common formulations (e.g., nasal, suppository).

Appendix 4.3: Operationalizing fracture hospitalizations

Outcome (PPV)[1]	**Definition**
Fracture composite endpoint	(Includes all outcomes defined below)
Femur (PPV: 87%)[127]	Hospitalization with ICD-9 CM femoral fracture diagnosis (821.XX)
Hip (PPV range: 86%-98%)[128]	Hospitalization with hip fracture diagnosis (ICD-9 CM: 820.XX) AND one of the following procedure codes during same hospitalization (ICD-9 CM: 78.55, 79.05, 79.15, 79.25, 79.35, 79.65; CPT: 27230-27248).
Humerus (PPV: 95%)[127]	Hospitalization with ICD-9 CM humerus fracture diagnosis (812.XX)
Pelvis (PPV: 93%)[127]	Hospitalization with ICD-9 CM pelvic fracture diagnosis (808.XX).
Radius/ulna (PPV: 96%)[127]	Hospitalization with ICD-9 CM radius fracture diagnosis (813.XX).

Abbreviation: PPV, positive predictive value

[1]The following studies guided our operationalization of fracture hospitalizations.[127–129]

Appendix 4.4: Crude and IPT-weighted baseline resident characteristics of nursing home residents in the 120 days before initiating oxycodone, hydrocodone, or tramadol (N=110,862 residents; 134,432 treatment episodes).

	Crude (Unweighted)				IPT-weighted[1]			
Characteristic	**Oxycodone**	**Hydrocodone**	**Tramadol**	**SMD[2]**	**Oxycodone**	**Hydrocodone**	**Tramadol**	**SMD[2]**
Number of treatment episodes[3]	14,373	69,182	50,877	-	14,339.7	69101.0	50,915.9	-
Demographics								
Age in years, mean(SD)	83.7 (8.8)	84.3 (8.6)	85.5 (8.4)	0.13	84.7 (8.5)	84.7 (8.5)	84.7 (8.5)	<0.01
Women, %	72.2	74.5	79.0	0.11	76.4	76.0	76.1	0.01
Race, %				0.08				0.03
Non-Hispanic white	81.0	83.5	84.5		85.3	84.1	83.9	
Non-Hispanic black	12.9	11.2	11.3		10.4	11.2	11.3	
Hispanic/Latino	4.5	3.3	3.0		2.8	3.2	3.2	
Other	1.6	1.9	1.2		1.5	1.6	1.6	
Married, %	17.5	17.2	15.6	0.03	16.9	16.7	16.6	0.01
Behavior, %								
Rejects care	10.2	10.1	9.9	0.01	9.9	10.1	10.0	<0.01
Wandering	5.0	6.4	6.4	0.04	6.1	6.2	6.3	0.01
Cognitive impairment,[4] %				0.08				0.02
No impairment	32.4	28.3	29.5		30.2	29.4	29.4	
Mildly impaired	23.7	23.6	24.0		24.6	23.8	23.8	
Moderately impaired	33.6	38.1	37.2		36.2	37.1	37.1	
Severely impaired	10.3	10.1	9.2		9.0	9.7	9.7	
Inattention, %				0.04				0.02
None	82.2	79,9	80.2		81.6	80.4	80.4	
Intermittently present	10.0	11.0	11.2		10.5	10.9	10.9	
Continuously present	7.8	9.0	8.6		8.0	8.7	8.7	
Disorganized thinking, %				0.04				0.02
None	83.5	81.5	81.6		82.4	81.8	81.9	
Intermittently present	9.5	10.6	10.8		10.6	10.6	10.4	
Continuously present	7.0	7.9	7.6		7.0	7.6	7.6	
Overall Physical functioning,[5] %				0.10				0.01
No/minimal assistance	21.1	25.7	26.6		25.7	25.7	25.6	
Requires extensive assistance	55.1	53.1	53.9		54.0	53.6	53.6	
Physical dependence	23.8	21.2	19.5		20.3	20.7	20.8	
Physical functioning – transfers,%				0.11				0.02
Independent	11.5	13.5	14.5		14.1	13.7	13.7	
Supervision required	8.5	9.6	10.1		9.3	9.7	9.7	
Limited assistance required	14.1	15.1	15.7		15.6	15.3	15.3	
Extensive assistance required	47.6	45.0	45.6		45.5	45.5	45.5	
Total dependence	18.4	16.8	14.1		15.4	`15.8	15.9	
Physical functioning – locomotion on unit				0.08				0.02

Independent	19.5	21.0	21.4		21.5	21.1	21.0	
Supervision required	16.6	17.3	18.2		16.9	17.6	17.6	
Limited assistance required	14.3	15.4	15.6		15.4	15.3	15.3	
Extensive assistance required	26.8	26.1	26.2		26.8	26.3	26.2	
Total dependence	22.8	20.2	18.6		19.4	19.7	19.9	
Physical functioning – locomotion off unit				0.10				0.03
Independent	14.8	16.9	16.8		17.4	16.8	16.6	
Supervision required	14.1	15.7	16.1		14.5	15.7	15.7	
Limited assistance required	12.1	13.7	13.6		13.7	13.5	13.5	
Extensive assistance required	22.8	24.0	23.7		24.2	23.8	23.7	
Total dependence	36.2	29.7	29.9		30.2	30.3	30.4	
Pain,[6] %				0.06				0.02
No self-reported or staff-assessed pain	68.0	70.6	71.3		69.3	70.3	70.3	
Any self-reported pain	28.1	25.3	25.4		27.0	26.0	26.0	
Any staff-assessed pain	3.8	4.1	3.3		3.73.7	3.8	3.7	
Urinary incontinence, %				0.11				0.01
Always continent	21.8	22.2	24.0		22.9	22.9	22.9	
Occasionally incontinent	15.1	17.0	18.2		17.3	17.3	17.3	
Frequently incontinent	28.2	28.9	30.1		29.9	29.4	29.3	
Always incontinent	35.0	31.9	27.7		29.8	30.5	30.6	
Bowel incontinence, %				0.09				0.02
Always continent	40.1	42.3	45.4		43.7	43.4	43.3	
Occasionally incontinent	12.0	12.5	12.8		13.1	12.6	12.6	
Frequently incontinent	18.1	17.2	17.6		17.7	17.4	17.4	
Always incontinent	29.8	28.0	27.7		25.6	26.5	27.7	
Mobility devices normally used, %								
Cane/walker	45.0	44.0	48.4	0.06	46.9	45.9	45.8	0.01
Wheelchair	79.4	75.6	73.9	0.09	76.6	75.3	75.2	0.02
Oxygen use, %	9.4	9.2	8.4	0.02	9.5	9.0	9.0	0.01
Unplanned weight loss, %	4.6	4.5	4.3	0.01	4.8	4.4	4.4	0.01
Comorbidities, %								
Dementia	56.2	59.6	60.6	0.06	58.1	59.4	59.5	0.02
History of falls	21.0	23.4	23.1	0.04	23.3	23.1	23.1	<0.01
Previous fracture	3.9	2.9	2.7	0.04	3.2	3.0	3.0	0.01
Parkinson’s disease	6.8	7.4	7.2	0.02	7.3	7.2	7.3	<0.01
Seizures / epilepsy	8.2	8.2	6.1	0.05	7.4	7.4	7.3	<0.01
Paralysis	10.8	9.8	8.1	0.06	9.5	9.2	9.3	0.01
Osteoporosis	18.5	18.5	19.6	0.02	18.8	18.9	19.0	<0.01
Arthritis	30.2	30.1	33.5	0.05	32.0	31.7	31.6	0.01

Pressure ulcers	5.5	3.9	3.3	0.07	3.7	3.8	3.9	0.01
Hypertension	77.7	77.3	78.0	0.01	77.0	77.5	77.5	0.01
Congestive heart failure	21.5	21.0	20.7	0.01	21.4	21.0	21.0	0.01
Coronary artery disease	22.8	18.9	20.8	0.06	20.0	20.2	20.2	<0.01
Peripheral vascular disease	11.7	9.2	9.8	0.06	9.8	9.7	9.6	<0.01
Dysrhythmia	18.3	16.6	17.3	0.03	18.0	17.2	17.1	0.02
Stroke	17.6	17.6	16.7	0.02	17.6	17.2	17.2	0.01
Diabetes	35.0	34.5	31.5	0.05	33.4	33.4	33.5	<0.01
Hyperlipidemia	38.2	36.8	37.1	0.02	37.2	37.0	37.1	<0.01
Thyroid disorder	20.1	21.3	22.2	0.03	22.6	21.7	21.7	0.02
Renal insufficiency/renal failure/ESRD	10.3	8.9	8.9	0.03	9.2	9.1	9.1	<0.01
Asthma/COPD/chronic lung failure	20.9	19.6	19.2	0.03	20.4	19.7	19.8	0.01
Shortness of breath	10.0	10.2	9.7	0.01	10.5	10.1	10.2	0.01
Anxiety	25.7	28.0	27.5	0.03	28.4	27.8	27.7	0.01
Depression	57.2	56.6	55.2	0.03	56.8	56.4	56.3	0.01
Number of medications prescribed, median (P25-P75)	9 (7-13)	9 (7-13)	9 (6-12)	0.04	9 (7-13)	9 (6-13)	9 (6-13)	0.02
Psychotropic medications, %								
≥2 psychotropic medications prescribed[7]	32.2	33.1	30.9	0.03	32.5	32.3	32.3	<0.01
Antipsychotics	25.1	26.7	25.8	0.02	25.5	26.2	26.2	0.01
Antidepressants								
SSRI	42.6	42.8	40.6	0.04	42.6	42.2	42.2	0.01
SNRI	8.7	8.1	7.1	0.03	8.1	7.8	7.8	0.01
Tricyclics	2.0	2.2	1.9	0.01	1.9	2.1	2.1	0.01
Other	26.7	22.9	25.1	0.06	24.7	24.1	24.0	0.01
Anxiolytics[8]	20.1	21.3	19.6		21.0	20.7	20.6	0.01
Hypnotics[8]	5.6	5.7	5.1		6.0	5.5	5.5	0.01
Pain adjuvant medications, %								
Anticonvulsants	18.8	15.8	14.1	0.09	15.9	15.6	15.7	0.01
Systemic corticosteroids	8.7	7.7	7.9	0.02	8.2	7.9	7.9	0.01
Nonsteroidal anti-inflammatory drugs	11.7	11.9	13.1	0.03	12.3	12.4	12.7	0.01
Skeletal muscle relaxants	5.6	4.3	3.8	0.06	4.7	4.3	4.4	0.01
Other medications associated with falls or fractures								
Anticonvulsants (not used as adjuvants)	9.5	9.1	6.8	0.06	8.4	8.3	8.2	<0.01
Antimuscarinics (for urinary retention)	9.2	10.3	10.4	0.03	11.2	10.3	10.3	0.02
Cardiovascular medications								
Alpha blockers	5.7	6.2	5.4	0.02	6.2	5.9	5.9	0.01
Antiarrhythmics	3.3	3.6	3.7	0.01	3.5	3.6	3.6	<0.01

Anticoagulants	15.3	13.4	13.3	0.04	13.5	13.6	13.6	<0.01
Antiplatelets	10.4	11.0	10.7	0.01	11.0	10.9	10.9	<0.01
ACE inhibitors	5.5	6.7	6.3	0.03	6.2	6.4	6.4	<0.01
ARB	10.0	10.6	11.2	0.03	10.5	10.8	10.9	0.01
Beta blockers	45.3	40.4	42.1	0.07	42.5	41.7	41.6	0.01
Calcium channel blockers	28.4	27.4	28.7	0.02	28.2	28.0	28.0	<0.01
Digoxin	5.9	6.3	6.2	0.01	6.4	6.2	6.2	0.01
Loop diuretics	35.3	36.8	36.9	0.01	37.9	36.9	36.9	0.02
Potassium sparing diuretics	5.1	5.5	5.5	0.01	5.3	5.4	5.5	0.01
Thiazide diuretics	8.7	9.8	10.1	0.03	9.4	9.8	9.8	0.01
Statins	37.5	35.2	35.2	0.03	35.2	35.4	35.5	<0.01
Nitrate	10.2	10.2	10.0	0.01	10.5	10.2	10.2	0.01
Diabetic medications								
Insulin or other injected hypoglycemics	20.6	20.1	16.9	0.06	19.4	18.9	19.0	0.01
Sulfonylureas	8.0	8.9	8.7	0.02	8.4	8.8	8.8	0.01
Other oral diabetic medications	11.4	12.2	11.6	0.02	11.3	11.9	12.0	0.01
Gastric medications								
H2 antagonists	6.8	6.5	5.9	0.02	6.6	6.4	6.3	0.01
Proton pump inhibitors	29.7	31.7	30.5	0.03	32.5	31.2	31.2	0.02
Dementia medications								
Memantine	13.6	18.1	18.1	0.08	16.9	17.6	17.6	0.01
Cholinesterase inhibitors	22.9	28.4	28.9	0.09	27.5	28.0	27.9	0.01
Osteoporosis medications	8.3	8.9	9.0	0.02	9.4	8.9	8.9	0.01
Parkinson's medications	9.6	10.7	10.0	0.02	10.5	10.4	10.5	<0.01

Abbreviations: ACE: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blocker; COPD: congestive obstructive pulmonary disease; ESRD: end-stage renal disease; P25-P75: 25th to 75th percentile; IPT: inverse probability of treatment; SD: standard deviation; SMD: standardized mean difference; SNRI: selective norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitor.

[1]The mean of the stabilized IPT-weights was 1.00 (minimum: 0.16 , maximum: 8.65)

[2]SMDs were summarized by averaging the pairwise differences between treatment groups. See Appendix 4.6 for further detail on pairwise SMDs before and after IPT-weighting.

[3]110,862 residents contributed 134,432 treatment initiation episodes (17.0% of residents contributed >1 treatment episodes [range: 2-6]). Treatment switching was uncommon: 2.4% and 0.01% of residents initiated 2 or 3 different treatments, respectively.

[4]Cognive impairment was defined using the Cognitive Function Scale (CFS; range 0-3):[134] cognitively intact (0), mild impairment (1), moderate impairment (2), and severe impairment.

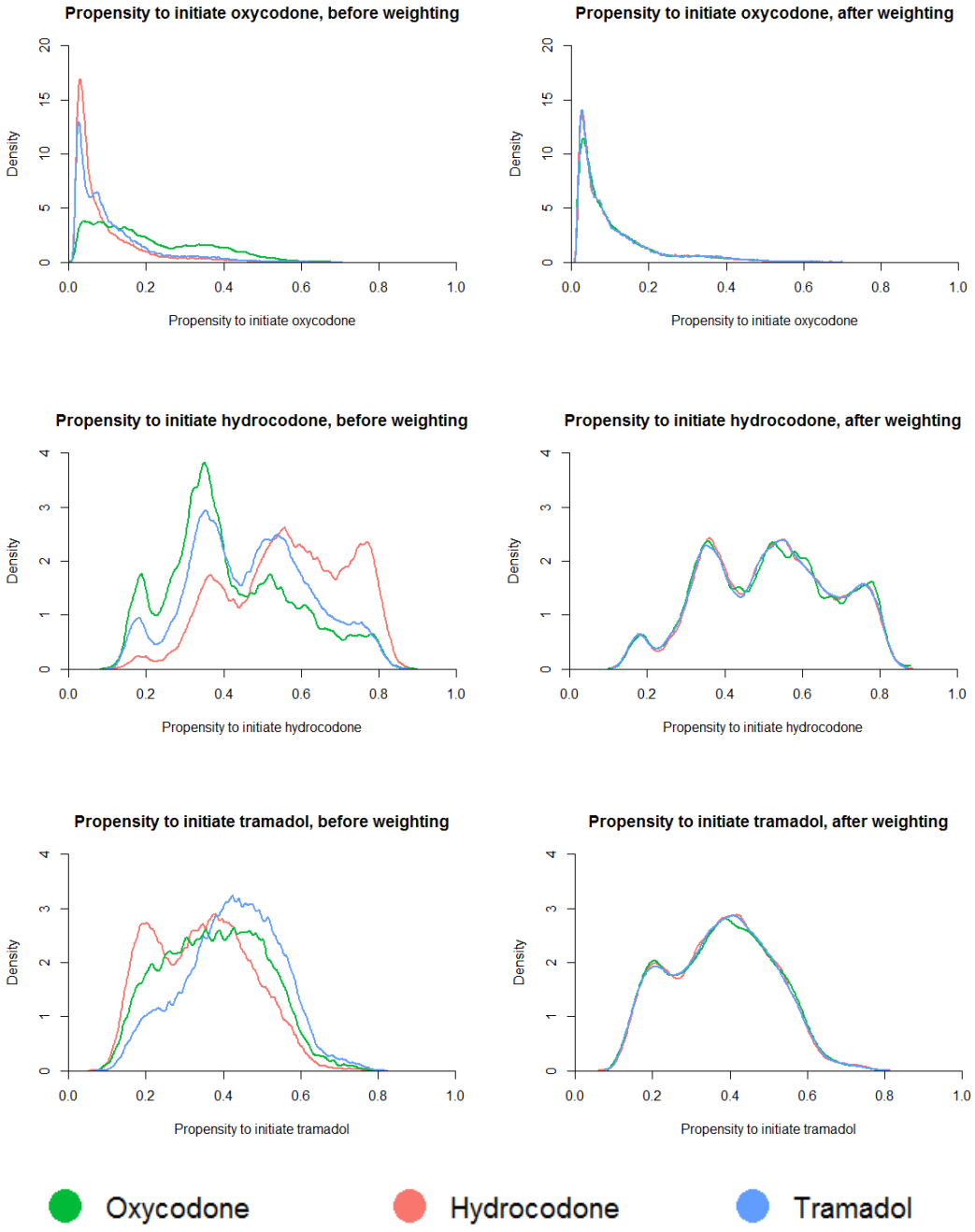
[5]Physical limitations were defined using the Activities of Daily Living Self-Performance Hierarchy (range: 0-6):[90] no/mild limitations (0-2), extensive limitations (3-4), and physical dependence (5-6).

[6]Resident pain in the five days preceding the most recent Minimum Data Set (MDS) assessment before treatment initiation was based on self-report when the resident was able to and staff assessment otherwise.

[7]Based on antipsychotics, antidepressants, anxiolytics, and hypnotics

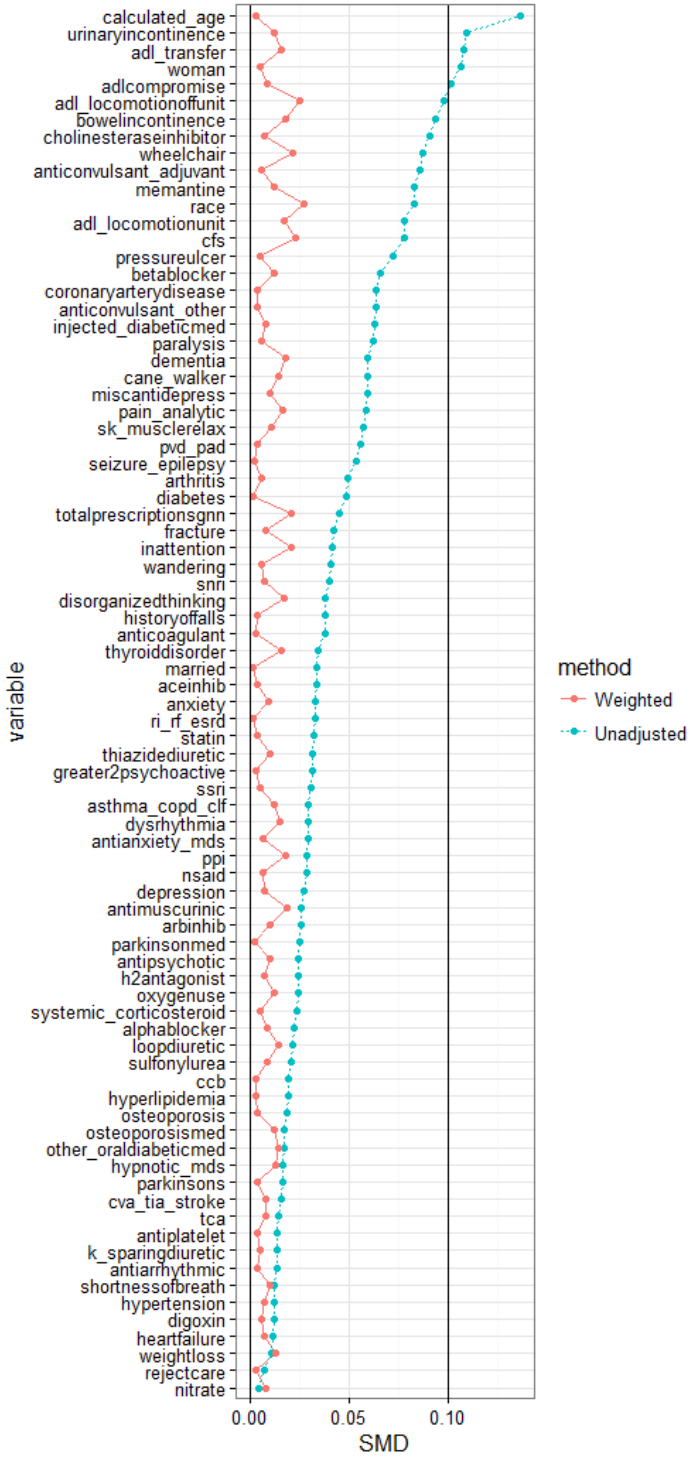
[8]Anxiolytics and hypnotics were measured in the seven days before the most recent MDS assessment because benzodiazepines were not covered by Part D in 2011-2012.

Appendix 4.5: Distributions of propensity scorers for each study drug before and after inverse probability of treatment weighting.



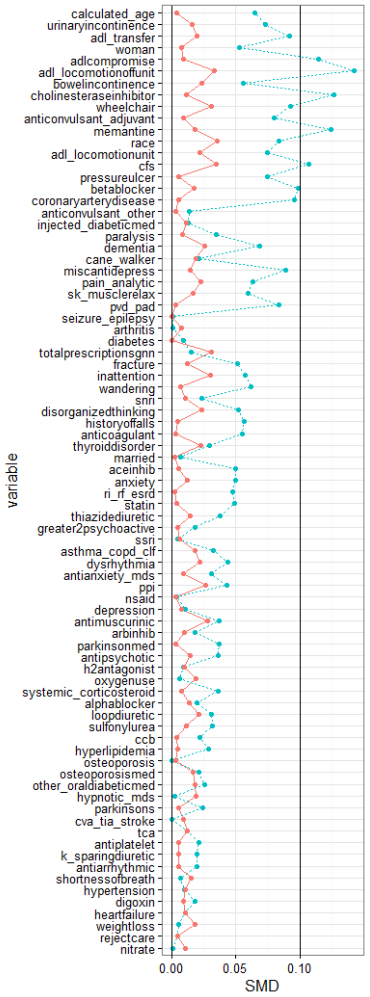
Appendix. 4.6: Overall and pairwise standardized mean differences of baseline resident characteristics before and after inverse probability of treatment weighting.

Overall:

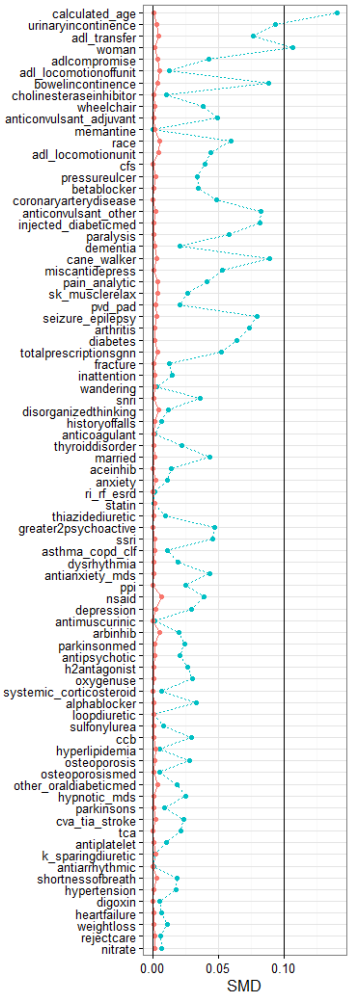


Pairwise:

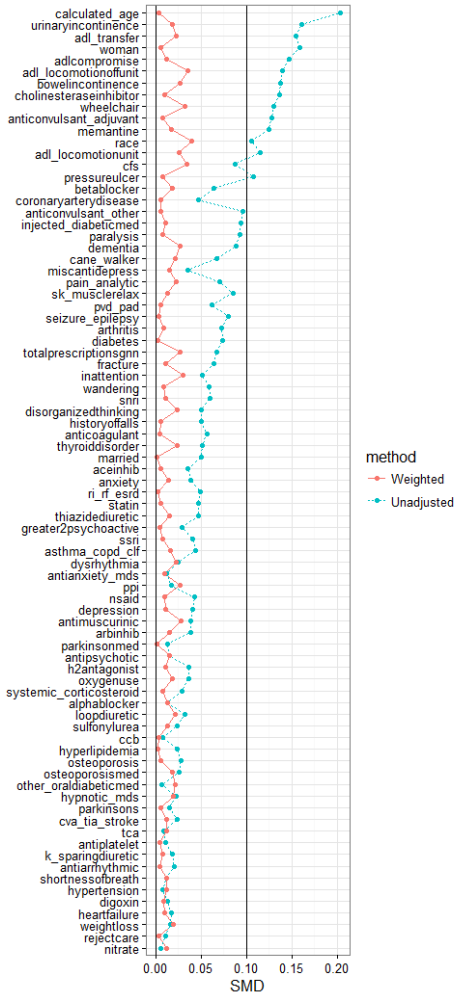
Oxycodone and Hydrocodone



Tramadol and Hydrocodone

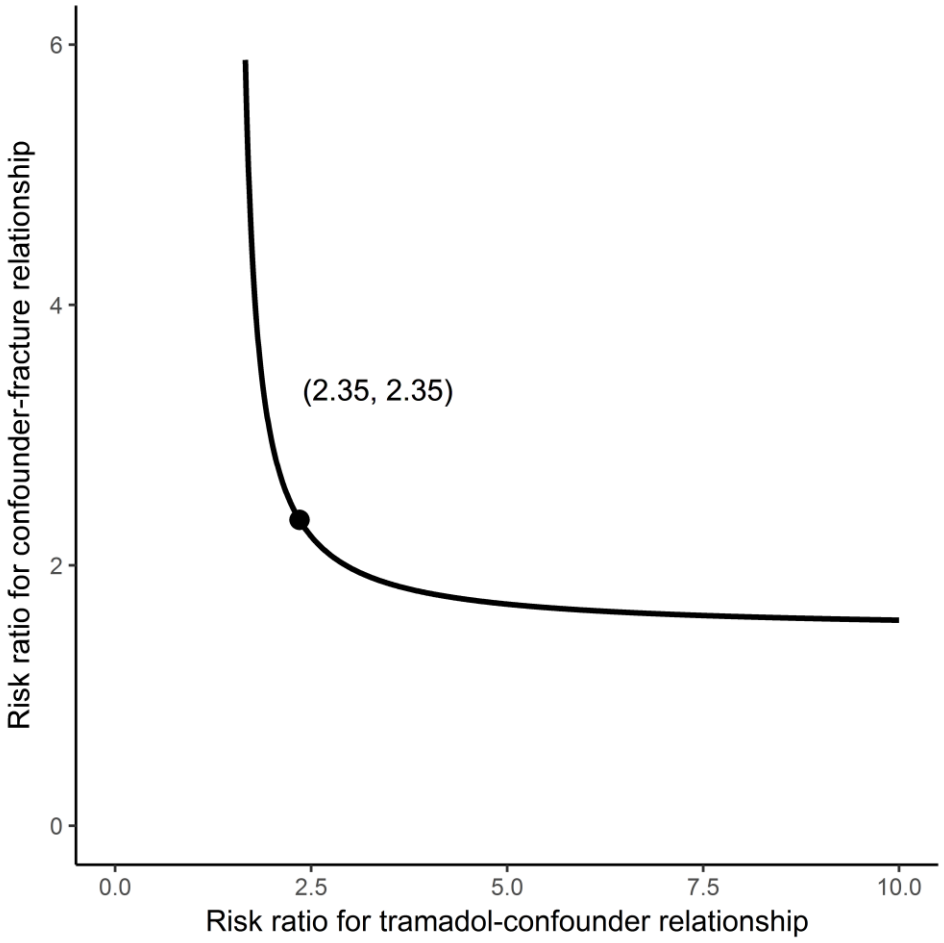


Oxycodone and Tramadol

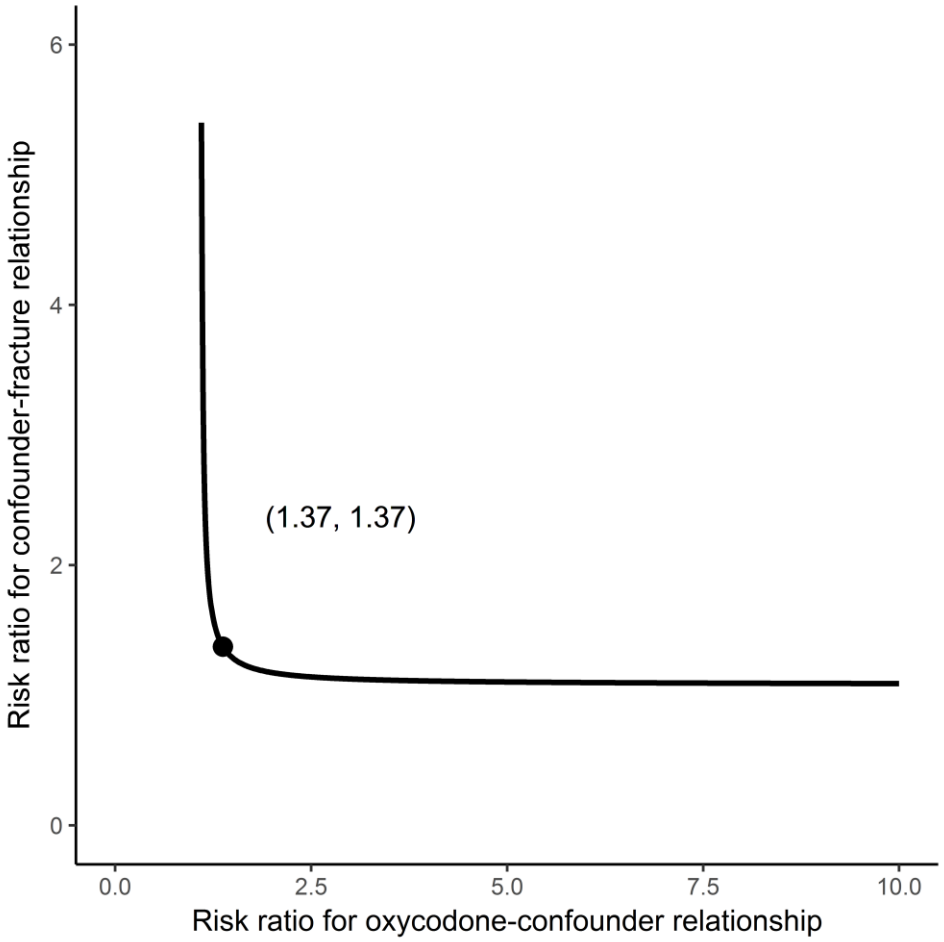


Appendix 4.7: Bias analysis for unmeasured confounder

The minimum strength an unmeasured confounder would have to be on the risk ratio scale to attenuate the observed association of tramadol and fracture hospitalizations (subdistribution hazard ratio=0.67 in primary as-treated analysis) to 1.0. Note: an unmeasured confounder with a risk ratio of 1.81 could move the upper 95% confidence interval of 0.80 to 1.0.



The minimum strength an unmeasured confounder would have to be to attenuate the observed association of tramadol and fracture hospitalizations (subdistribution hazards ratio=1.08 in primary as-treated analysis) to 1.0. Note: lower confidence interval crosses one in primary analysis.



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